NHS
Research and
Development Forum

Local Capacity and Capability for Research

Introductory Essentials
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www.rdforum.nhs.uk

NHS Research and Development Forum

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NHS
Research and
Development Forum

About the Forum

The Forum is a professional network and community of practice for the NHS health and care research management, support, and leadership workforce.

It is easy to become a member you just need to sign up to our mailing list to receive current news.
http://www.rdforum.nhs.uk/content/membership/

Being a member is free as we meet our running costs by raising income through events, and as we are a non-profit organisation this income also supports Forum activities for the benefit of the community. All of our resources are accessible via our website because we believe in collaboration and open access for all.

How to become involved

It is easy to become involved in the Forum. Here are some of the ways you can contribute:

- ✓ Feed into consultation responses
- ✓ Join a working group or project
- ✓ Lead a task & finish group to solve a problem
- ✓ Contribute resources to the resources exchange
- ✓ Request or support peer review
- ✓ Become a Forum trainer
- ✓ **Attend a Forum training course or event**
- ✓ Help to develop a course
- ✓ Join the conference programme planning committee
- ✓ Join the conversation on social media
- ✓ Write a blog
- ✓ Offer to provide support to others

NHS
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Useful Links

Follow on Twitter @NHSRDFORUM

Forum Resources Exchange:
https://rdforum.nhs.uk/resource-exchange/

Glossary & Dictionaries

The 'GET IT' Glossary: Plain language definitions of research terms
http://getitglossary.org

Forum Contacts: info@rdforum.org.uk
kate.greenwood@rdforum.org.uk

Trainer Contacts:

allyson.bailey@nhs.scot

Welcome to "Local Capacity and Capability for Research"

About the course

The course is designed to provide an understanding of the requirements of an NHS organisation when determining whether to take part in a particular research study as a host. It explains the principles of good study set up, the information required by the R&D office and where it can be obtained. It introduces delegates to the various systems and documents associated with research and also provide some guidance on developing relationships with key support departments and stakeholders within an NHS organisation. The course is particularly useful for staff who are new to a capacity and capability review role, but can also provide a review/reassurance for those with more experience.

The first half of the day concentrates on making delegates familiar with process. The second half is spent putting everything into practice working through an example study.

Course objectives

At the end of the course you will:

1. Understand the process and importance of feasibility assessment

2. Understand the questions to be asked/information to be collected when undertaking a local assessment

3. Be familiar with the study documents and sources of information from which information is collected

About the workbook:

This book should principally be used as a reference guide for all the topics we cover in the course. You should aim to stay up to date by following the news and social media feeds of the NHS R&D Forum but also that of regulators, networks and policy makers and search the Forum resources exchange.

This book is also a workbook with activities and pages for completion during the course. You can use it to record your reflections and to help you manage your next steps**.**

Thank you for joining us.

Agenda	
9:00-9:15	**Log-in and online platform information**
	Introductions and course overview.
	Importance of local assessment
	Feasibility and site selection
	Local assessment 1
10:15-10:45	**Break**
	Local assessment 2
	Sources of information
12:30-1:15	**Lunch**
	Local assessment exercise: read and assess documentation
2:30-3:00	**Break**
	Local assessment exercise: discussion
4:30-5:00	**Q&A, evaluation and close**

IMPORTANCE OF ROBUST LOCAL ASSESSMENT OF LOCAL CAPACITY AND CAPABILITY

Many research projects carried out within the NHS/HSC have implications for local capacity and carries resource implications. You need to understand and confirm everything that is required for taking part and establish whether your organisation has the capacity to undertake the work; whether your staff have the appropriate knowledge, skills and training, whether you have the necessary facilities and equipment and whether you have a sufficient pool of potential participants to enable you to deliver on your recruitment target.

Failure to do so can have a number of consequences for your site:

- Exposing your patients or staff or the organisation to unnecessary risk
- Wasting limited resources and money
- Damaging your reputation and reducing your chances of attracting future research

It also has implications for the sponsor and the study as a whole:

- Not recruiting enough participants or including incomplete or incorrect data can invalidate the whole study
- Wasting limited resources and money, which could have been used for a site that would deliver appropriately

It is therefore in everyone's best interest to spend the time doing an effective yet proportionate local assessment of the whether or not your organisation can deliver this type of study before taking the process any farther forward.

One of the most important but also hardest requirements for assessing the "fit" of a study in your organisation is actually getting to know your organisation. Who does what, who has responsibility/sign off for what, where do you go for information or support? It's definitely worth investing in some two way awareness raising across your organisation to make contacts and get everyone on board.

There are some legal or procedural differences across the four UK nations. For example, the law concerning adults with a mental incapacity is different in Scotland than it is in England. These issues should all be dealt with at study-wide review level, but if the study you are considering is crossing a border, just be aware of this.

HRA and HCRW definitions of the steps involved in local set up:

- **Assessing** whether the NHS organisation has the capacity and capability to participate
- **Arranging** practical steps to provide the capacity and capability
- **Confirming** that the NHS organisation has the capacity and capability to deliver the study and will do so

Scotland and Northern Ireland follow much the same process although some of the language is currently different (ie, "approve" rather than "confirm").

Feasibility

FEASIBILITY REVIEW OR ASSESSING IF IT IS LIKELY THAT YOUR ORGANISATION WILL BE ABLE TO DELIVER THE STUDY

What do we mean by Feasibility review or assessment?

- Pre-study assessment of 'do-ability'
- Sometimes follows Expression of Interest

- Most often done as a formal process for commercial studies, though is sometimes done for non-commercial. You may also do it in a less formal way if your PI or organisation is told about a study prior to starting the full capacity and capability process.

Helps to identify potential issues early

- Is there likely to be capacity to carry out all procedures?
- Do we have the required equipment (or could be get access to it)?
- Do we have the appropriate staff?
- Does the site do things the same way as the protocol requires?
- Is the recruitment target achievable?
- Who will support site set up?
- What is your local Principal Investigator's background, previous experience and research interest?
- What is the patient population and recruitment estimate?
- Are there any "competing" studies at your site?
- Have all areas been given opportunity to comment
- What else?.....

Note: sponsors should approach potential sites as soon as the CI starts writing protocol to ensure that the study is "doable" in the NHS/HSC at all. Lead NHS/HSC R&D offices have a key role is supporting this activity in collaboration with sponsors.

For host sites:

  - PI and/ or R&D office approached by sponsor[1] (ideally the PI, R&D Office and any supporting research network should be simultaneously contacted by the sponsor so that all can contribute to the process
  - First, establish if there are any local investigators interested
  - Check that you actually treat that condition at your site (paediatrics, oncology...)
  - Provide information on possible recruitment, facilities available, lab reference ranges etc
- Important to be realistic---don't say you can recruit 50 patients when you can really only recruit 10.
- Be honest on likely time-lines to study set up. It is better to say no or that we would not be in a position to open for 6 months so the sponsor can look at management of the project.
- Sometimes sponsor may arrange a site visit to see the investigators and facilities for themselves
- For some study types the sponsor will not provide a form or a formal process but will simply ask you to make an assessment of whether or not you could potentially take part in this study.
- **It is really important that this stage is conducted very quickly Some sponsors may ask for a 24 or 48 hour turnaround**
  - It allows you to say no as quickly as possible
  - It shows the sponsor that you know your site and you can be proactive in working with them

RESPONDING TO A FEASIBILITY DOES NOT COMMIT YOU TO ACTUALLY TAKING PART IN THE STUDY

[1] Throughout this course, "sponsor" is used as shorthand for whoever you at the local participating site deal with in discussing whether you can take part in the study. It could be the sponsor representative, CI, study coordinator or CRA.

SITE SELECTION

- Once the feasibility questionnaire is returned you may not have a response for some time. Most companies don't let you know if you have NOT been selected
- There may be a separate Site Selection visit.
- Once your site has been selected, the set up processes can begin and should be undertaken to the timetable the sponsor would like to achieve

When your site has been selected this stops being theoretical. You now begin the work to put in place the study set up arrangements

ACTIVITY: Read through the feasibility request below and answer the following questions:

1. Who would you want to discuss the request with?

2. What issues do you need to consider in deciding whether/how to respond?

(Note: this feasibility request is based on a real study. Certain information has been removed/anonymised to protect commercial confidentiality)

Study summary:

- A placebo-controlled Phase II study to evaluate efficacy, safety and tolerability of Investigational Medicinal Product (IMP).
- The main objective of the study is to assess whether the IP delays progression of XX utilizing MDS-UPDRS as the outcome measure.
- Study targets participants with a diagnosis of XX who are not on any treatment. MOA-B inhibitors are allowed. Diagnosis will be confirmed in all subjects by brain DaT SPECT scan, obtained within 1 year or at screening.
- The study medications will be taken orally once daily for 40 weeks.
- A subset of subjects will have SPECT DaT scans both at baseline and week 40 as a marker of neuronal health.
- To evaluate the effect of the IP on CSF biomarkers, 3 lumbar punctures will be performed over the course of the study (at Baseline, 8 weeks, and 40 weeks).

Key Questions:

1. Do you have an interested PI?
2. Do you see potential participants with a diagnosis of XX at your site/practice?
3. Considering the inclusion criteria and expectation of 3 LPs over the course of the study, how many patients would you be able to enrol over 6 months?
4. How many patients would you be able to enrol over 12 months?
5. Do you routinely use DaT/SPECT scans for confirmation of diagnosis?
6. Do you have access to single photon emission computed tomography (SPECT) on site?
7. Do you have dedicated staff and facilities to handle Radiopharmaceutical products on site?
8. Would the use of Radiopharmaceutical agents as diagnosis method be a barrier to conduct a clinical trial at your site/country?

Local Arrangements

PUTTING ARRANGEMENTS IN PLACE IN ORDER TO CONFIRM LOCAL CAPABILITY ANDCAPACITY

Peer review, NHS REC, other authorisations and UK study-wide review ensure the study is scientifically, ethically and financially sound.

- In England and Wales, sites cannot confirm capacity and capability until HRA and HCRW Approval is in place
- In Scotland and Northern Ireland, sites cannot approve until study wide review is in place

However, for most studies there will be local arrangements to be put in place in order to deliver the study. You can begin considering these while awaiting final study wide review/approval.

The local arrangements may vary considerably from those in the CI's organisation.
Confirmation of capacity and capability (England and Wales) or local approval (Scotland and NI) can only be given when everyone involved at the participating organisation is satisfied they can deliver the study.

Every study and every site is different. Not every study will require the same breadth and depth of activities to put in place the arrangements. It is important to remain proportionate in your approach and consider the level and type of risk involved.

Different people will have different roles in this process as well. Some may take an active part in putting appropriate arrangements in place while others may simply be providing information or confirming site readiness.

THINGS TO CONSIDER:

- **Who is doing what to whom...**
- **Where, when, how often and for how long**
- Need details of
    - All staff involved
    - Number and type(s)of participants expected
    - Visits, procedures, investigations
    - Facilities and equipment required
    - Often forgotten: stationery, postage, packing, telephone calls
- Are staff appropriately trained, qualified and experienced? Will they require specific training?
- Do any of the staff have conflicts of interest that might preclude them taking part?
- Do you have the necessary facilities and equipment AND do they have the capacity to accommodate the research activity?
- What activity is additional to normal, standard care and what will the cost and cost attribution of this be?
- What activity may be done differently from standard? ie, will samples be sent to a central lab rather than being analysed locally?
- What emergency/out of hours/back up procedures might be required?

If you have done a feasibility exercise you should already have answers to some of these.

Consider who you need to liaise with to support the study set up and confirm capacity and capability. It's really important to develop relationships with all research active/interested groups so that together everyone can help deliver the study to national as well sponsor expectation!

Participants and Activities Involving Participants

Local recruitment:

- Target, start/end date?
- Is target achievable in the time?
- Remember that if the target is detailed in an agreement, you have legally contracted to reach that target (usually using "reasonable endeavours").

Does the study involve participants? These types of study do not:

- Studies only involving patient data
- Studies only involving patient tissue
- Studies of services or processes

Who are the participants?

- Patients
- Relatives/carers
- Controls
- Staff
- You may need to assess each group separately if their journey through the study is different—patients may go through all the interventional visits while relatives only complete a questionnaire
- Will any of the participants be adults with a mental incapacity (permanent or temporary), children, prisoners, other special/vulnerable groups?
- Any special arrangements required at site (translation, security etc)?

How will participants be identified? Including details of data sources

- By clinical staff from local records/clinic lists
- Advertisements/self referral
- From existing sources—research database, professional network
- By another participant—a patient may nominate their carer

By whom will they be identified-NHS/HSC or external staff?

- Who is having access to participants' details?
- Would they normally have access?
- Have the participants consented to this?
- Are there confidentiality issues?
- Is there a need for Confidentiality Advisory Group (CAG--England), Public Benefit Privacy Panel (PBPP—Scotland) or Privacy Advisory Committee (PAC—Northern Ireland)?

Who CAN identify participants?

- Specialist knowledge required? Certain professions?

Local PIC activity

- Is site really a PIC? SITE TO CONFIRM. Sponsors sometimes claim a site is a PIC when they are actually carrying out protocol-driven activities. It is possible to be a satellite or other type of site. This requires the full assessment and agreement to take part, even if you are not taking part in the entire study.
- The actual part the organisation is playing in the study should be clear from the Local Information Pack

How will participants be contacted/informed about study?

- By clinical team at appointment

- Advertisements
- Letter, email, text, telephone call
- Are there any confidentiality issues? The patient may not have told their family about the condition, so is there a risk that someone could see the email or letter?
- Are there issues around the patient's well being, particularly if they are being invited outside the clinical setting? Could the invitation be upsetting?
- Who will contact/inform?

Consent – in a study where consent is sought, a robust process is absolutely vital

- How will participants be consented? Face to face, remotely by email or post, online, implicit consent (completing and returning a questionnaire)
- When will they be consented? Do participants have to give consent at the same time as they are informed about the study? If not, what time to they have to consider?
- Is an extra visit required? Will this be an issue for the participants and/or the service? (will a room be available, has the visited been costed)
- Who CAN take consent? Does it need to be a doctor/dentist or some other specific person?
- Who WILL take consent? Are there enough appropriate people on the team to cover whenever consenting might be required, including holidays, sickness, out of hours
- Arrangements for proxy consent/assent? Adults with a mental incapacity, children, emergency research in patients who may be unconscious
- Special considerations for consent: participants newly diagnosed with a serious condition, children, vulnerable participants, relatives/carers consenting for a seriously ill or injured relative...
- Is there enough time allotted for participants to read, understand and ask questions about the information and for the appropriate member(s) of the team to take consent?

The consent form details all activities to be undertaken by participants (examinations, medical procedures, questionnaires, focus groups, interviews). This is a large part of how you will put the arrangements in place to ensure that you have the capacity and capability to deliver the study. If you cannot then you need to say so early.

R&D Offices have a key role in facilitating getting the arrangements in place working with the individual departments across the whole organisation.

The sponsor and CI will have made certain assumptions about the participants and their clinical journey but the process may be quite different in your organisation. It is important to ensure either that your patient pathways will allow you to follow the protocol or that the sponsor is willing to make an amendment to allow you to take part. Consider the following and think about how you will work with the delivery teams to put in place the arrangements to enable the study. Who would you need to work with to make it happen?

- When will each activity take place? Think about both the participant (blood test every 6 weeks) and the team/service (blood tests are fasting so appointment must be made for first thing in the morning).
- How frequently does each happen?
- How long does each last, both individually (assessments will take 1 hour per visit) and across the study (assessments will take place 6 monthly for 5 years)?
- Are there particular time constraints for any activity? For example, the blood test must be taken an hour before treatment or treatment must begin within 6 hours of diagnosis?
- Where does each one take place?
- Are NHS/HSC facilities required? Which and for how long? Will this involve extra travel for participants? If your organisation doesn't have dedicated research facilities, ensure you have clear

agreement to use clinical rooms, equipment etc and that these will be available when needed for the research visits.

- Will staff be going to participants' homes? Security arrangements for home visits? Do you need to arrange for lone worker training?
- Will activities take place anywhere else? Another NHS/HSC or private facility or a university? Be aware of the possible issues around movement of data outside the NHS/HSC, indemnity arrangements (particularly if any clinical activities are happening outside the NHS/HSC) or contractual/financial agreements
- What happens if participants are moved during the study, for example from ICU to a HDU or a ward?
- What comfort arrangements are needed for participants: beds/chairs, entertainment, refreshments?
- Which activities are standard care and which are additional/extra? Standard care can vary from site to site. The site must confirm what is standard there. This may affect the costing/payments for the study. Remember that there will be a centralised cost review carried out for the study, so you don't have to duplicate that work
- Does the site have the appropriate staff/facilities/equipment to carry out each activity? If not, can the sponsor provide support or does the site have to contract with another NHS/HSC or external organisation? This will have contractual and/or financial implications.
- Who will carry out each activity? Are particular professions required (mobility assessment must be carried out by a physiotherapist)? Is training in a particular skill/technique required? Will the sponsor provide this?
- Will external staff be coming into the organisation to carry out any of the activities? What contractual arrangements, if any, are needed including Research Passports, honorary research contracts and/or letters of access? The site must confirm where Honorary Research Contracts or Letters of Access are required. Commercial staff, including monitors, are generally covered under the site agreement.
- Will any special equipment be required for any of the activities? **See "Medical Devices and Equipment" below for a list of questions/requirements.**

- **Don't forget the "follow-up" portion of the study, which in some cases could last many years**

Data

- Can you meet the requirements of the protocol regarding data collected, recorded transferred and archived.
- Details of data being collected, particularly about participants-what information, when, from where
- By whom is it being collected—internal staff (who would routinely have access) or external?
- Have the participants consented to this?
- Are there confidentiality issues?
- If participants have not given prior consent, the central review should have identified the need for approval from the appropriate bodies (CAG,PBPP, PAC)
- How will it be recorded, anonymised, transferred, stored, used, archived and/or destroyed?
- Is personal data leaving the site? Have participants consented?
- Local involvement in data collection-staff/time/facilities required to pull notes, access/transcribe/send/analyse data, archiving/destruction arrangements.
- Will there be data linkage with external/national datasets? This may require separate CAG,PBPP, PAC approval

Other participant related activities carried out by the local team

- Randomisation process—will team have access to phones, computers to access randomisation system?
- Completion of CRF/eCRF – do you need to set up any IT systems to record information in e-CRF
- What monitoring/cover is required between visits and/or out of hours? Can the site provide this?
- SAE and other recording/reporting requirements. Remember the "24 hour" rule for SAEs.

- What team input is likely to be required for monitoring?
- Other participant related activities?
    - Training participants to use equipment.
    - Administering or assisting with questionnaires or assessments/measures.
    - Physical exam/measurements.

Drug or treatment administration by study team

- Dispensing/delivery process including timings-when does pharmacy get request, time frame within which drug must be administered, number of patients, frequency of dispensing, day(s) of week and time(s) of day if known or if certain ones are required etc.
- How are drugs supplied/administered to participants? Do they need to be monitored? When, where, by whom, for how long?
- Facilities required to administer/monitor?
- Who can carry out each of the above? Particular training required to deliver drug?
- Equipment required-fridge, freezer, temperature logging, temperature controlled transport, equipment for administering drugs

Miscellaneous activities/costs:

- Photocopying/printing
- Stationery
- Postage
- Telephone calls/texts
- Staff travel time/costs for home visits, attending different facilities, escorting participants

Pharmacy

- Work with pharmacy to facility their review of capacity and capability. Ensure the sponsor has provided the technical assurance review, pharmacy manual and associated documents (see https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/technical-assurances/pharmacy-assurance/). These should cover much of the information below:
- Are any of the drugs extra/different to standard care? Standard care varies from site to site, so the site must determine.
- What drugs will be used?
- How will they be supplied to site? Details of ordering, shipping, delivery, receipt, return and/or destruction.
- Special/separate storage required? Temperature controls? How much stock will be supplied each time? What size storage is required? For commercial studies, there is a payment for oversized storage.
- Will drugs be kept in Pharmacy or in ward/department? If stored outside Pharmacy, how much, for how long, where? What are the temperature/security requirements? Are both Pharmacy and the sponsor satisfied with what is being provided? Risk assessment
- What does pharmacy have to do-label, make up, etc?
- Special/aseptic facilities required?
- Details of label supplied. Can additional labels be added?
- Logs and reconciliation processes including return/destruction
- Out of hours procedures/requirements-temperature excursions, unblinding
- Who can carry out the activities above? Pharmacist, pharmacy technician? Ensure there are back up staff to cover for holidays, sickness etc.

Remember that a study may include several different drugs or placebo treatments with different requirements!

Labs and pathology

Work with departments to facility their review of capacity and capability. Ensure the sponsor has provided the lab manual and any associated documents. Ensure you have all details for each type of sample—some may be processed locally while others go to a central lab, or all may go to a central lab but some are sent immediately while others are frozen to be shipped in batches.

- What type of samples will be taken? Blood sample, tissue biopsy, urine
- How many will be taken from each participant, at each visit and across the study. The participant needs to know how many and how much will be taken (2 tablespoons of blood, a skin sample 0.5cm in diameter etc.)
- When and where will they be taken? During routine care or is an extra visit required?
- Will the samples be surplus from standard ones--some extra blood taken during a routine blood draw, or a small portion of a tumour separated when it is removed—or additional/specific to the research?
- Who CAN take them? Is specialist knowledge or training required? Who WILL take them? Are there enough people on the team to cover whatever is required?
- How much and what type of equipment/consumables will be required? (Needles, containers, etc) A single blood sample may need to go into several different containers.
  Will they be supplied to site? If not, remember to consider the cost of the equipment used for research specific activities.
- If samples are leaving the organisation, have participants consented? What is the anonymisation process? Is a Material Transfer Agreement required? Some sponsors request that an MTA is put in place even when the participants have consented. It is definitely needed if the participants are NOT consenting, especially if there is not a study agreement. (there is an MTA as part of the OID)
- Which samples will be shipped?
- When will they be sent-immediately or will they be stored/batched?
- How will they be shipped? Post/courier? Are packing/postage supplied? If not, these costs need to be factored in. What is the shipping procedure? If a courier is being used, what are the details? What is the sponsor's QA of the shipping process? Normally the site's responsibility ends once the material has left the premises, but you still want to be sure it will arrive in good condition.
- Is any on-site processing required? Aliquoting, spinning? A single blood sample may need to be divided into several different containers, each of which could require different handling or processing. How many are likely to require each type of processing-overall and at any one time? Who will handle/process the samples?
- For samples that will be sent to the local lab, when will they go to the lab and how quickly must they be dealt with? Is there a time constraint for results? For example, are a participant's TFTs and LFTs required before they can have the next treatment? How quickly (realistically) can the labs turn this around? What hours are they available to operate? What happens if a patient comes in out of hours?
- Where on site tests are to be carried out-
  - what tests,
  - when,
  - how many (per participant and at any one time)?
  - Can site do them or is external contractor/another NHS/HSC site needed?
- If samples are to be stored on site, what are the requirements? Refrigeration, freezing? What temperature(s)? Length of time? Number of samples (overall and at any one time)? Is there enough room to store the expected number of samples? What are the back-up plans if storage equipment breaks down?
- Is information on local equipment, lab ranges etc required?
- What reporting is required on samples and results? Is it extra/different to routine reporting? This will need to e quantified. How often will reports be needed? Who will be producing the reports? Is any

special training required? When will reports be required—as above, are there time constraints? Can the labs meet these?
- Will stored samples to be supplied? What type and how many (altogether and at any one time)?
- Are they stored on site or will they need to be sent/retrieved from another facility? What is the retrieval process? Is there a cost for this?
- Who will retrieve, process, and send the samples?
- What are the return/storage/destruction arrangements of samples? Often research samples may not be used to destruction and so the sponsors may wish to store them for future research. Are the participants aware of what may happen to the samples? Have they consented to it?
- **For ALL samples, which of the above activities is standard and which is extra? SITE TO CONFIRM**
- For all samples, will any special equipment be required for any of the activities? **See "Medical Devices and Equipment" below for a list of questions/requirements.**

Imaging (https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/technical-assurances/radiation-assurance/)

Work with the department to facility their review of capacity and capability. Ensure you have details for each type of imaging. Not all organisations have the equipment to carry out every type of image (X-ray, MRI, CT, PET).

- Type of imaging
- When, how often and where will it take place? Can site do it or is external contractor/another NHS/HSC site needed?
- What is standard and what is extra-SITE TO CONFIRM
- WHO can do it
- What reporting is required on images? Is it extra/different to routine reporting? This will need to be quantified. How often will reports be needed? Who will be producing the reports? Is any special training required? When will reports be required— as per the example in the sample section above, are there time constraints? Can the local team meet these?
- Will images be sent away? Have participants consented to this? What is the anonymisation procedure? If physical hard copies are being sent, will packing/shipping/postage be provided?
- If the participant is being exposed to radiation for research (even if they would have had the same exposure in normal care) IRMER (Ionising Radiation (Medical Exposure) Regulations) sign off is required by the local Clinical Radiation Expert (CRE) and Medical Physics Expert. NOT needed for MRI or ultrasound
- Is information on local equipment required? Type/model of equipment, outputs etc

Radiation Exposure/Administration

- The sponsor needs Administration of Radioactive Substances Advisory Committee (ARSAC) approval if the protocol involves administering radioactive substances OR specifies the frequency, activity or processing of a dose that would otherwise be standard care.
- The site (and a relevant practitioner at the site) may require an ARSAC licence which covers use of the procedures involved for research purposes. Does site have these?
- Details of type, duration and frequency of exposure. Standard or extra? SITE TO CONFIRM-standard care can vary from site to site. Refer to the Radiation Technical Assurance
- Can site carry it out or is another contractor/NHS/HSC site needed? Not all organisations have the equipment/facilities to deliver these treatments. If participants would need to go elsewhere, consider travel time and costs. Will the sponsor contract directly with the other site or will a sub contract/pass through payments be needed?

Medical Devices and Equipment for studies

Most studies will only be looking at one device, but if there is more than one ensure you have the information for each.

- What device is involved?
- Is it licensed/CE marked? If not, the study -wide review should confirm that MHRA approval is in place
- How will it be supplied? Will it be a gift or loan?
- Who is responsible/arrangements for procurement, delivery, set up, calibration, maintenance, consumables, repair, return if required?
- Is supplier on NHS/HSC Master Indemnity Agreement list? If so, an indemnity agreement delivery note may be required if these issues are not covered in the study agreement. If they are not on the list, not, they will have to complete a Standard Indemnity form. (this should be covered by the central study-wide review)
- If the equipment is coming in contact with patients/participants, it will need to be checked/approved by Medical Physics
- What are the power requirements? Will there be any implications if there is a power interruption/failure?
- Will the device need to be connected to the local IT system/network? Approval will be needed from IT/eHealth and possibly Information Governance
- What is the size/configuration of the equipment? Is there an appropriate secure space for it?
- Does it require any special environment such as a temperature controlled area?

IT/eHealth

- Will the study require any new programmes to be installed on the local system? Have these been fully validated?
- Will the study require material to be uploaded to/downloaded from the Internet? What are the security, virus protection etc arrangements?
- Will the study require any moveable media such as USB devices to be linked to your organisations' computers or other equipment? What are the security/encryption arrangements?

Other departments/support required

Ensure you identify and quantify any input required by areas of the organisation not detailed above, for example:

- Medical Records pulling/retrieving notes
- Patient transport or taxi services
- Porters or estates

R&D Office and oversight activities

Contacts

- Details of sponsor and funder.
- Contact details of sponsor representative or coordinating centre for discussions about local set up, contracts etc. There may be different people dealing with different aspects of the study—ensure that you are getting consistent information.
- Details of local team: PI, local collaborator, research nurse(s) etc.
- Will there be any topic specific network/speciality group involvement or support?
- Details of any sub contractors or other organisations involved

Study details and local governance

- Study type, phase

- Ensure you have the most recent approved versions of all relevant documents, especially if joining the study late. Note that SoE/SoECAT may not have been updated
- Length of study and length of local involvement—both end of recruitment and end of follow up, if applicable
- Where is the study based within the organisation (especially for Health Boards): acute hospitals, primary care, community, tertiary centres, prisons? Some may take place across several locations.
- Will primary care or other facilities be contracting separately with the sponsor?
- When/how often is site likely to be monitored? This can change throughout the life of the study
- Will monitoring be on site or remote or a mixture?
- What will a visiting monitor need? Hard copies, print outs of electronic information, visits to any departments? Have you identified a suitable place for monitoring visits?
- If the monitor requires access to electronic records can s/he be given access to the system? What security is available to ensure they don't access anything inappropriately?
- How long is each visit likely to last? This can also vary throughout the study?
- Who needs to attend each visit? Consider the cost and capacity implications
- Remote monitoring-information to be supplied, format, frequency?
- What type of information is to be supplied for remote monitoring? Is any of it identifiable? If so, have the participants consented? What are the security arrangements?
- What monitoring/oversight of the study will your organisation undertake?
- What are the archiving arrangements for the study? How much material is likely to be generated? Is here any archiving payment?
- Any different arrangements needed for other UK nations where there may be legal differences from lead site? SITE TO CONFIRM
- Are ALL support departments aware of activity/implications and have agreed? Agreement confirmed in writing if required?
- What are the arrangements to report/confirm recruitment
- What are the local archiving arrangements, if needed?
- GCP or other training required for local staff, including Health and Safety? For whom? Push back on requirement for GCP training for non-CTIMPs. It is more important that people understand the principles than have a certificate (see the MHRA/HRA joint statement on GCP training: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/)
- Protocol specific training-who requires what? When/how provided? Time, duration, location, frequency?
- Does the study cross over into shared or integrated services such as prisons, schools or social care? If so, ensure all parties have agreed on governance and financial arrangements.
- Contracts/agreements
- The template agreement for the study will be approved by the lead R&D coordinating centre. However, you will want to check that it is suitable for your site, particularly the study specific items and be aware of the various provisions that have been agreed centrally:
    - If the sponsor is not using a standard template, have the modifications or reason for doing so been detailed and agreed by the central reviewer?
    - Are there equitable arrangements for responsibility and indemnity? When, how and by whom the agreement can be terminated?
    - The governing law
    - What are the intellectual property arrangements?
    - Has the sponsor used a standard costing template? This should always be requested. If not, how are prices determined?
- Is your site satisfied with
    - The recruitment target

  - The arrangements in the event of the PI leaving
  - The list of site responsibilities
  - The study milestones
  - The financial arrangements
  - The supply arrangements
- Financial arrangements
- Have you clearly determined which staff are carrying out which activities, the time involved and the number of times each will be carried out, to allow you to calculate the your costs?
- Some activities may only happen in certain circumstances such as a patient needing an extra scan if they show certain signs or symptoms. Be aware of the possibility of these costs being incurred and what the "worst case" maximum cost could be for your organisation.
- Non-commercial Portfolio studies should have all costs "attributed" using the AcoRD guidance https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research
  - Research costs (Part A, if Association of Medical Research Charities (AMRC) funded) should be funded by the study grant or award. Is there any arrangement to say these to the site? If you are joining a study late the grant funding may have been exhausted, in which case you may need to absorb the costs.
  - Service Support costs. What information do you need to collect to ensure that this activity is included in the calculation for your allocation? (these should come through in the SOECAT)
  - Treatment costs are paid by the NHS/HSC. The local departments that will incur these costs should be aware of and agree to them. There should be an assumption that if cost neutral or cheaper they will take part unless there are clear capacity or safety issues.
  - Excess Treatment Costs—that is, treatment costs that are substantially more expensive than standard care. There may be funding available to cover some of these. You must have accurate information on treatment cost activity to calculate whether you are eligible to apply for an ETC subvention. This information should be included in the SOECAT. Do you know your application process?
- Commercial research MUST pay for all research activity—the NHS/HSC cannot subsidise commercial work. Hence the need to fully and accurately detail all local activity so that it can be costed. This allows discussion with the commercial sponsor to ensure full funding.
- Is there any other funding available to the site? Some non-Portfolio studies may provide funding to cover certain costs.
- What are the invoicing/payment schedule arrangements?
- Is VAT payable? As a general rule, income from overseas or from a grant (even if your organisation is not one of the grant holders) and also income from a non-eligible body that is related to patient care are all VAT exempt.
  Income from a charitable or other eligible body such as a university or government body or income from a non eligible organisation THAT IS NOT RELATED TO PATIENT CARE, attracts the standard rate of VAT.
  Are there any "payments in kind" or cost savings/avoidance? Where drugs are supplied your organisation does not have to fund normal treatment.
- Will participant travel or other expenses be paid? How do they claim/get refund?

SOURCES OF INFORMATION

The answers to many of the questions above will be available from the various documents associated with the study. It makes sense to extract as much as possible from the documents, then discuss any ambiguities, contradictions or gaps with the sponsor.

- Protocol
    - Will detail all aspects of the study
    - May have visit chart listing all participant procedures
    - Should have details of sponsor contacts
    - Language may be too technical for non-clinicians
- Investigators Brochure/Summary of Medical Product Characteristics (IB/SMPC) -technical details about trial drug(s)
- IRAS application
    - Will explain all procedures and, generically, who will carry them out
    - Proposed end date/length of study as a whole – not at your site
- Patient Information Sheet
    - Very useful for finding out exactly what will happen to participants
    - Must be in "lay" language so easier for non-clinical R&D staff to understand
- Schedule of Events/SoECAT/commercial budget
    - Breaks down all study events per visit
    - Useful starting point because it details ALL local activity
    - Also provides attribution for eligibly funded studies
- Organisation Information Document
    - Captures details of local activities, dates, local staff involved, costs/payments, training, material transfer, confidentiality and data issues, signatures and template delegation log
    - Details agreed between site and sponsor
    - Can also be used as site agreement

SOMETIMES THE DOCUMENTS MAY CONTRADICT EACH OTHER (this should have been picked up by the REC or the Assessor/study wide reviewer. If not refer to your national coordinating function) The protocol mentions two scans but the PIS only mentions one; or the IRAS form says there are three extra visits but the local information you have mentions four. Check with the sponsor for confirmation. An amendment may need to be made to make everything consistent.

- The paperwork can't tell you everything. It is important to have clear discussions with the sponsor, local research team, support departments, finance, other organisations and anyone else who will be involved in the study

- The sponsor can confirm
    - Exactly what you will be expected to do
    - What they will provide/supply and on what terms
    - Any other support they will provide—training, funding, staff etc
    - All study procedures
- You may find yourself dealing with one person for set up and another for contracts, for example. It is important to ensure that everyone agrees to what is being proposed.
- Where there are gaps or contradictions in the information provided to you, it is the sponsor's responsibility to provide authoritative information. Always request this in writing to allow you to refer back if there is ever a question about it.
- Your local research team has the clinical expertise to assess the protocol and decide whether it is appropriate for your organisation and if you will be able to deliver. They can also provide
    - Details of background, training, skills and experience
    - CVs and GCP certificates-you should retain these for active investigators so you don't have to ask for them each time and can also remind them when updates are needed.

    - Information on local arrangements: are your clinics scheduled/organised as assumed in the protocol?
- Local support departments can provide
    - Lab reference ranges
    - Details of local equipment and facilities
    - Confirmation of capacity and capability to take part
- You should also get Finance and legal review support if required for the study.

Getting the local arrangements right ensures that you should be able to deliver on your promises and contribute to a successful study.

★ Putting in place the arrangements for a study will depend on the complexity of the study. It is important to be proportionate so the study is set up as quickly as possible. Don't repeat checks undertaken by other authorities and regulators.

When you know that HRA and HCRW Approval (for England and Wales) or UK study wide review (for Scotland and Northern Ireland) is in place and you are content that you can deliver the study you can issue Confirmation of Capacity and Capability (for England and Wales) or approval (Scotland and NI) through execution of the contract or agreement or issuing an appropriate letter.

This means that your organisation is ready and able to commence research project activities.

a) Immediately, or

b) After the SIV and/or when the sponsor says start (or gives green light)

In practical terms this means that from the NHS/HSC organisation perspective all of their arrangements are in place that are needed to start the study and arrangements to ensure that as the study progresses the organisation will continue to be able to deliver the study are in hand. It is the commitment to start whenever the sponsor is ready to do so (eg after SIV/green light/drug shipping, etc.).

For example, if the required research nurse is being recruited and the participating NHS/HSC cannot start until this has happened then confirmation of capacity and capability cannot be issued. However if you can rejig the workforce to get started knowing that the recruitment process is in hand then you can.

It is good practice for the sponsor (or their nominated representative) to then confirm with the site the date the project activities can start, if this has not already been communicated.

Final Exercise

Final Exercise

Activity: You have been provided with a series of documents from a research study. Read through these and carry out, as far as possible, a local capacity and capability assessment. Answer the following questions:

1. How long will the study last overall, how long will participants be involved and how many participants will be recruited?

2. What are the activities at the
- Screening visit
- Randomisation/infusion visit
- Visits 1-13

3. What will happen to the blood samples?

4. any other issues with the study or the documents you have identified?

Who would you want to discuss the arrangements with – including which support departments?

What issues do you need to consider in putting in place the arrangements?

Who undertakes the final sign-off?

How are all parties notified that site is confirmed?

Study documents 1/7: Protocol

THE STUDY

PROTOCOL VERSION NUMBER AND DATE

Version 1.3 (11/02/2016)

RESEARCH REFERENCE NUMBERS

IRAS Number:

EudraCT Number:

ISRCTN Number / Clinical trials.gov Number:

SPONSORS Number:

FUNDERS Number:

SIGNATURE PAGE: REMOVED FOR TRAINING

KEY TRIAL CONTACTS

Chief Investigator

Trial Co-ordination

Co-Sponsor

Co-sponsor

Funder(s)

Clinical Trials Unit

Key Protocol Contributors

Statistician

Trials pharmacist

TRIAL SUMMARY

Trial Title	THE STUDY	
Internal ref. no. (or short title)		
Clinical Phase	Phase 4	
Trial Design	Prospective Randomised Open, Blinded End-point (PROBE)	
Trial Participants	Patients with chronic heart failure (CHF) secondary to left ventricular systolic dysfunction and iron deficiency	
Planned Sample Size	1000	
Treatment duration	Average of 3 years (event driven trial, expected maximum 4.5 years, minimum 2.5 years – anticipated 2 years recruitment and a projected further 2.5 years of treatment/assessments, giving a range of projected patient participation of 2.5 – 4.5 years). This includes End of Study visit.	
Follow up duration	Minimum of 2.5 years follow-up from last patient recruited	
Planned Trial Period	Approximately 4.5 years	
	Objectives	Outcome Measures
Primary	To compare the additional effect of an intravenous (IV) iron regimen with standard guideline-indicated therapy on cardiovascular (CV) mortality and hospitalisations due to heart failure in patients with CHF secondary to left ventricular systolic dysfunction and iron deficiency.	CV mortality or hospitalisation for worsening heart failure (analysis will include first and recurrent hospitalisations)
Investigational Medicinal Product(s)	Iron isomaltoside-1000	
Formulation, Dose, Route of Administration	Iron isomaltoside-1000 (100 mg/ml) as an infusion over 15-30 minutes up to a maximum of 20 mg / kg	

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
British Heart Foundation	
Drug company	- Provision of investigational medicinal product, bio-bank and additional contribution to research costs.

ROLE OF STUDY SPONSOR AND FUNDER

XXX and YYY will be Co-sponsors of the trial. Prior to study initiation, a non-commercially funded clinical trial co-sponsorship agreement will be put in place between XXX and YYY. The roles and liabilities each organisation will take under The Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2001:1031 are laid out in this agreement signed by both organisations. YYY shall be responsible for carrying out the obligations and responsibilities set out in the aforementioned agreement, and shall be deemed "sponsor" for the purposes of, Part 3 of the regulations in relation to the study. XXX shall be responsible for carrying out the responsibilities set out in the agreement, and shall be deemed "sponsor" for the purposes of, Parts 4, 5, 6 and 7 of the Regulations in relation to the study.

The Co-Sponsors will delegate specific roles to the Chief Investigator, CTU and other third parties. These arrangements will be clearly documented in agreements and/or the Sponsor Delegated Roles and Responsibilities Matrix.

<u>British Heart Foundation (BHF)</u>

The study has been funded in part by a grant from the BHF. The BHF has a representative on the Trial Steering Committee (TSC) but does not have a designated role or responsibility in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. An annual report in relation to progress of the trial will be submitted to the BHF. Support from the BHF will be acknowledged in any publications related to the study.

<u>Drug Company</u>

This is an investigator-initiated study. Drug Company have provided support in terms of the investigational medicinal product (IMP) and additional financial support. Drug Company does not have a designated role or responsibility in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. A representative from Drug Company will be invited to attend TSC meetings as an observer. Support from Drug Company will be acknowledged in any publications related to the study.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

REMOVED FOR TRAINING

KEY WORDS: Chronic heart failure

Iron deficiency

Left ventricular systolic dysfunction

PROBE design

Intravenous iron

LIST of CONTENTS REMOVED FOR TRAINING

LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
BHF	British Heart Foundation
BNP	B-type Natriuretic Peptide
CA	Competent Authority
CEC	Clinical Endpoint Committee
CHF	Chronic Heart Failure
CHI	Community Health Index
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CRT-D	Cardiac Resynchronisation Therapy Defibrillator
CRT-P	Cardiac Resynchronisation Therapy Pacemaker
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
CTIMP	Clinical Trial of Investigational Medicinal Product
CV	Cardiovascular
CVA	Cerebrovascular Accident
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
ECG	Electrocardiogram

eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated Glomerular Filtration Rate
EMEA	European Medicines Agency
ESA	Erythropoietin Stimulating Agent
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GDG	Guideline Development Group
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GU	Genitourinary
Hb	Haemoglobin
HF	Heart Failure
IB	Investigator Brochure
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
IV	Intravenous
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MA	Marketing Authorisation

MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
MS	Member State
NHS GG&C	National Health Service Greater Glasgow & Clyde
NHS R&D	National Health Service Research & Development
NICE	The National Institute for Health and Care Excellence
NIMP	Non-Investigational Medicinal Product
NSAID	Non-Steroidal Anti-Inflammatory Drug
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPM	Permanent Pacemaker
PROBE	Prospective Randomised Open-label Blinded Endpoint
PV	Pharmacovigilance
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QoL	Quality of Life
QP	Qualified Person
RCT	Randomised Control Trial
RDW	Red blood cell Distribution Width
REC	Research Ethics Committee

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
TSAT	Transferrin saturation
UKKRC	UK Kidney Research Consortium

TRIAL FLOW CHART

Basic entry criteria
Patient with CHF: pre-discharge (after admission for HF), recent inpatient (within 6/12) or stable out-patient

Inclusion criteria

1. Age ≥18 years
2. LVEF <45% within the last 6 months using any conventional imaging modality
3. New York Heart Association (NYHA) class II–IV
4. Iron deficient - defined as TSAT <20% and/or ferritin <100 ug/L
5. Evidence of being in a higher risk HF group:
   1. Current (with intention to discharge in next 48 hours) or recent (within 6 months) hospitalisation for HF, **or**
   2. Out-patients with NT-proBNP >250 ng/L in sinus rhythm or >1,000 ng/L in atrial fibrillation (or BNP of > 75 pg/mL or 300 pg/mL, respectively)
6. Able and willing to provide informed consent

Exclusion criteria

1. Haematological criteria: ferritin >400ug/L; Hb <9.0 or >13 g/dL in women or >14g/dL in men; (B12 or folate deficiency should be corrected but do not exclude the patient)
2. MDRD eGFR <15ml/min/1.73m^2
3. Chronic defined need for IV iron therapy
4. Likely to need or already receiving ESA
5. Planned cardiac surgery or revascularisation or cardiac device implantation; within 3 months of a primary diagnosis of type 1 myocardial infarction (excluding small troponin elevations in the context of heart failure admissions), cerebrovascular accident (CVA), major CV surgery or percutaneous coronary intervention (PCI), cardiac device implantation or blood transfusion; on active cardiac transplant list; left ventricular assist device implanted
6. Any of the following comorbidities: active infection (if the patient is suffering from a significant ongoing infection as judged by the investigator recruitment should be postponed until the infection has passed or is controlled by antibiotics), other disease with life expectancy of <2 years, active clinically relevant bleeding in the investigators opinion, known or suspected gastro-intestinal malignancy
7. Pregnancy, women of childbearing potential (i.e. continuing menstrual cycle) not using effective contraception or breast-feeding women
8. Contra-indication to IV iron according to current approved Summary of Product Characteristics: hypersensitivity to the active substance, to Monofer® or any of its excipients (water for injections, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment)); known serious hypersensitivity to other parenteral iron products; non-iron deficiency anaemia (e.g. haemolytic anaemia); iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis); decompensated liver cirrhosis and hepatitis
9. Participation in another intervention study involving a drug or device within the past 90 days (co-enrolment in observational studies is permitted)

Patient information sheet

Screening Visit: Informed consent, demographics, medical history, medication, clinical exam, TSAT, N-BNP#, ferritin, creatinine/eGFR, Hb, ECG, Inclusion/exclusion
Only required if out-patient & no admission in prior 6m

Randomisation/Infusion Visit: clinical exam, creatinine/eGFR, Hb, MCV, MCHC, MCH, RDW, platelets, sodium, potassium, urea, CRP, bilirubin^, albumin^, random glucose^, walk test, EQ-5D, Minnesota Living With Heart Failure Questionnaire, pregnancy test (if required), blood for central storage (sub study only), injection reactions, SAEs and Events of Special Interest, Inclusion/exclusion
^ If available

650 patients treated with iron isomaltoside 1000
Infused over min. of 15 mins for doses up to and including 1000mg, and min. of 30 mins for doses >1000mg
Body weight <50 kg: 20 mg/kg
Hb ≥10 g/dL and body weight 50 to <70 kg: 1000 mg
Hb ≥10 g/dL and body weight ≥70 kg: 20 mg/kg up to a max of 1500 mg
Hb < 10 g/dL and body weight 50 to <70 kg: 20 mg/kg
Hb < 10 g/dL and body weight ≥70 kg: 20 mg/kg up to a max of 2000 mg

650 patients treated with standard care

- Visit 1 (4 weeks after baseline)
- Visit 2 (4 months after baseline)
- Visit 3 (8 months after baseline)
- Visit 4 (12 months after baseline)
- Visit 5-13 (every 4 months from month 16 to 48)
- End of Study visit (date to be notified by CTU)

All Follow-Up Visits
- Blood samples will be collected either during the study visit or in advance of the visit (within 3 weeks) as part of standard clinical practice: TSAT, ferritin, creatinine/eGFR, Hb.
- Symptoms, SAEs, medication, clinical exam, EQ-5D, infusion & injection reactions

* Patients assigned to IV iron will be dosed if TSAT <25% and/or ferritin <100ug/L; redosing will not take place if ferritin >400 ug/L

Additional Assessments at 4 and 20 months
- MCV, MCHC, MCH, RDW, platelets, sodium, potassium, urea, CRP, bilirubin^, albumin^, random glucose^, bloods for central storage (sub study only)
^ If available
- Walk test
- Minnesota Living With Heart Failure Questionnaire

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SCHEDULE OF ASSESSMENTS

All visits should be performed within +/- 2 weeks of the documented visit time (e.g. 4 months +/- 2 weeks)

	Screening	Randomisation/ First Infusion	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7-13	End of study
Time from inclusion	*For hospitalised participants, these visits will be close together prior to discharge.* *For other participants randomisation should occur within 2 weeks of screening blood tests.*		4 weeks	4 months	8 months	12 months	16 months	20 months	24-48 months	*To be completed at participant's scheduled end of study visit. Visit date to be notified by the CTU on a patient by patient basis, LPLV is expected to be 4years and 4 months from first randomisation*
				Bloods will be collected either during the study visit or in advance of visit (within 3 weeks) as part of standard clinical practice, apart from blood for storage, which will be collected at the visit. Results must be available prior to any dosing visit.						
Consent	X									
Demographics	X									
Medical history	X									
Medications (baseline)	X									
Medications (concomitant)			X	X	X	X	X	X	X	X
Inclusion/ Exclusion	X	X								
Randomisation		X								
N-BNP	X*									

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	Screening	Randomisation/ First Infusion	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7-13	End of study
Time from inclusion	*For hospitalised participants, these visits will be close together prior to discharge.* *For other participants randomisation should occur within 2 weeks of screening blood tests.*		4 weeks	4 months	8 months	12 months	16 months	20 months	24-48 months	*To be completed at participant's scheduled end of study visit. Visit date to be notified by the CTU on a patient by patient basis, LPLV is expected to be 4years and 4 months from first randomisation*
				Bloods will be collected either during the study visit or in advance of visit (within 3 weeks) as part of standard clinical practice, apart from blood for storage, which will be collected at the visit. Results must be available prior to any dosing visit.						
TSAT	X		X**	X**	X**	X**	X**	X**	X**	
Ferritin	X		X**	X**	X**	X**	X**	X**	X**	
Creatinine/eGFR	X	X^^	X	X	X	X	X	X	X	
Haemoglobin		X^^	X	X	X	X	X	X		
MCV, MCHC, MCH, RDW		X^^		X				X		
Platelets		X^^		X				X		
Sodium, potassium, urea		X^^		X				X		
CRP		X^^		X				X		
Bilirubin^		X^^		X				X		
Albumin^		X^^		X				X		
Random glucose^		X^^		X				X		
Bloods for storage (sub study)		X		X				X		
Infusion **		X***	X***	X***	X***	X***	X***	X***	X***	

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	Screening	Randomisation/ First Infusion	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7-13	End of study
Time from inclusion	*For hospitalised participants, these visits will be close together prior to discharge.* *For other participants randomisation should occur within 2 weeks of screening blood tests.*		4 weeks	4 months	8 months	12 months	16 months	20 months	24-48 months	*To be completed at participant's scheduled end of study visit. Visit date to be notified by the CTU on a patient by patient basis, LPLV is expected to be 4years and 4 months from first randomisation*
				Bloods will be collected either during the study visit or in advance of visit (within 3 weeks) as part of standard clinical practice, apart from blood for storage, which will be collected at the visit. Results must be available prior to any dosing visit.						
Serious adverse events and events of special interest		X	X	X	X	X	X	X	X	X
Injection reactions		X**	X**	X**	X**	X**	X**	X**	X**	X**
Minnesota questionnaire		X		X				X		
EQ-5D		X	X	X	X	X	X	X	X	X
Clinical Assessment	X	X	X	X	X	X	X	X	X	X
6 minute walk test		X		X				X		
ECG+	X									
Pregnancy test++		X++	X++	X++	X++	X++	X++	X++	X++	X++

Notes:

1. X = assessments made as part of standard clinical practice for patients with chronic heart failure
2. X* = outpatients only without admission in last 6 months
3. X** = active treatment arm (iron) only i.e. 50% of recruits
4. ^ = if available
5. ^^ = use values from assessments within 2 weeks of randomisation if available
6. + = unless there are ECG results in the last 4 weeks prior to the visit
7. ++ = for women of child-bearing potential receiving IMP.
8. *** = infusion will only be given to those patients in the IV iron arm who meet the re-dosing criteria. If bloods tests taken at the study visit, a separate infusion visit within 3 weeks will be required for those who need re-dosing (anticipated approximately every third visit for those in IV iron arm). If blood tests available within the 3 weeks before study visit then re-dosing, if required, can happen at the main study visit.

Bloods will be collected either during the study visit or in advance of visit (within 2 weeks) as part of standard clinical practice. Results must be available prior to any dosing visit.

VISITS 7-13 will be held at the following intervals:

7=24 months, 8=28 months, 9=32 months, 10=36 months, 11=40 months, 12=44 months, 13=48 months

(Note a 'month' is defined as a calendar month.)

STUDY PROTOCOL

1 BACKGROUND-REMOVED FOR TRAINING

2 RATIONALE - REMOVED FOR TRAINING

2.1 Assessment and management of risk

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

Hypothesis

Addition of IV iron isomaltoside to guideline-indicated therapy for CHF reduces CV mortality and recurrent heart failure hospitalisation in patients with iron deficiency compared with guideline-indicated therapy alone.

Primary Objective

To compare the additional effect of an IV iron regimen with standard guideline-indicated therapy on CV mortality and hospitalisations due to heart failure in patients with CHF secondary to left ventricular systolic dysfunction and iron deficiency.

3.2 Secondary objectives

To compare the additional effect of an IV iron regimen to guideline-indicated therapy on all-cause mortality, other CV endpoints, QoL and assess its safety in patients with CHF secondary to left ventricular systolic dysfunction and iron deficiency.

3.3 Outcome measures/endpoints

3.3.1 Primary endpoint/outcome

CV mortality or hospitalisation for worsening heart failure (analysis will include first and recurrent hospitalisations) [18].

3.3.2 Secondary endpoints/outcomes- REMOVED FOR TRAINING

3.4 Exploratory endpoints/outcomes REMOVED FOR TRAINING

4 TRIAL DESIGN

This trial has a prospective, randomised open-label, blinded endpoint (PROBE) design. It will include parallel groups of participants who will be individually randomised. It is event driven and designed to assess the superiority of the addition of IV iron isomaltoside to guideline-indicated therapy as compared with guideline-indicated therapy alone for patients with CHF and iron deficiency.

5 STUDY SETTING

The study will be conducted across approximately 50 UK NHS secondary care institutions. The institutions will have the ability to give IV drug infusions and have appropriate resuscitation equipment available. All sites will need to be able to analyse serum ferritin and TSAT.

Participants will be identified from secondary care sites during or after hospitalisation (this will include local datasets), from outpatients and other local heart failure pathways (including

community services). The precise set-up of these heart failure services/pathways will vary according to locality. If a patient moves from the study site area they will have the possibility of being followed up in an alternative study site if feasible.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

1. Age ≥18 years
2. LVEF <45% within the last 6 months using any conventional imaging modality
3. New York Heart Association (NYHA) class II – IV
4. Iron deficient - defined as TSAT <20% and/or ferritin <100 ug/L
5. Evidence of being in a higher risk HF group:
    1. Current (with intention to discharge in next 48 hours) or recent (within 6 months) hospitalisation for HF, **or**
    2. Out-patients with NT-proBNP >250 ng/L in sinus rhythm or >1,000 ng/L in atrial fibrillation (or BNP of > 75 pg/mL or 300 pg/mL, respectively)
6. Able and willing to provide informed consent

6.2 Exclusion criteria

1. Haematological criteria: ferritin >400ug/L; haemoglobin <9.0, or >13 g/dL in women or >14g/dL in men; (B12 or folate deficiency should be corrected but do not exclude the patient)
2. MDRD estimated glomerular filtration rate (eGFR) <15ml/min/1.73m^2
3. Chronic defined need for IV iron therapy
4. Likely to need or already receiving erythropoiesis stimulating agents (ESA)
5. Planned cardiac surgery or revascularisation or cardiac device implantation; within 3 months of a primary diagnosis of type 1 myocardial infarction (excluding small troponin elevations in the context of heart failure admissions), cerebrovascular accident (CVA), major CV surgery or percutaneous coronary intervention (PCI), cardiac device implantation or blood transfusion; on active cardiac transplant list; left ventricular assist device implanted
6. Any of the following comorbidities: active infection (if the patient is suffering from a significant ongoing infection as judged by the investigator recruitment should be postponed until the infection has passed or is controlled by antibiotics), other disease with life expectancy of <2 years, active clinically relevant bleeding in the investigators opinion, known or suspected gastro-intestinal malignancy
7. Pregnancy, women of childbearing potential (i.e. continuing menstrual cycle) not using effective contraception (see Appendix 3) or breast-feeding women
8. Contra-indication to IV iron in the investigator's opinion according to current approved Summary of Product Characteristics: hypersensitivity to the active substance, to Monofer® or any of its excipients (water for injections, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment)); known serious hypersensitivity to other parenteral iron products; non-iron deficiency anaemia (e.g. haemolytic anaemia); iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis); decompensated liver cirrhosis and hepatitis
9. Participation in another intervention study involving a drug or device within the past 90 days (co-enrolment in observational studies is permitted)

7 TRIAL PROCEDURES

Also see schedule of assessments

7.1 Recruitment

7.1.1 Patient identification

Patients will be identified by a number of potential pathways:

1. In-patients with hospitalisation for heart failure
2. Heart failure hospitalisation within the last 6 months
3. Stable CHF patients identified in out-patient clinics/ heart failure services.

Patients with a diagnosis of heart failure will be pre-screened based on recent documentation of LVEF. Only patients with LVEF documented as <45% within 6 months will be approached to consider consenting to undergo formal screening and possible participation in the study.

For the purposes of the study, a current or recent hospitalisation for heart failure is defined as 'hospital admission with, or complicated by signs of, worsening heart failure that has resulted in the use of intravenous diuretics or a substantial increase in medication used to treat heart failure (for example increase in oral diuretics by 40 mg or more for furosemide or 1 mg or more for bumetanide or the addition of a thiazide like diuretic or the addition of a mineralocorticoid receptor antagonist)'. With an increasing utilization of ambulatory services, this will also include day care treatment to avoid admission (e.g. iv diuretics as day case).

It is anticipated that the majority of patients will be identified by the heart failure team (for example doctors, specialist heart failure nurses, heart failure pharmacists) directly involved in the care of the patients (including secondary care sites for both in and outpatients and community services). Patients may be under the care of different clinical teams. The initial approach to the patient will by the clinical team who are directly involved in their clinical care and permission sought to pass on their details to the research team (the research team will on occasions also be the clinical team).

Investigators should consider the cause of iron deficiency and the need for investigation according to guidelines and local practice. If further investigations or referral to another team for evaluation (e.g. gastroenterology) are thought necessary, the patient can still be recruited to the study prior to them taking place (i.e they can happen in parallel).

Potential participants may also be identified from local heart failure databases by the clinical and/or heart failure team. Initial contact with patients will be by the clinical and/or heart failure team to seek permission to pass on details to the research team.

Patients in hospital or attending clinics will be approached directly about potential participation in the study. Those identified through database searches will be contacted by letter and invited to indicate their willingness to take part by returning a reply slip in a provided stamped addressed envelope. Investigators will be permitted to issue up to 2 reminder letters a minimum of 3 weeks apart.
Regardless of the pathway, all patients will have at least 24 hours to review the patient information sheet before being approached for consent.

7.1.2 Screening

Standard clinical care for patients with CHF includes the assessment of LVEF and assessment and monitoring of haemoglobin and renal function. Assessment of LVEF will not be performed for the purposes of this study and patients will only be approached for formal screening if they have a documented LVEF <45% within the last 6 months (this will need to be within 6 months at the day of randomisation).

The majority of patients will have contemporary blood investigations. For screening purposes haemoglobin and eGFR assessed for clinical purposes within the last 4 weeks will be used (for patients in hospital or recently discharged frequent blood testing is generally performed for disease monitoring). If there are no recent blood test results available then consent must be obtained prior to blood samples being taken. For those who have consented, medical staff will assess and confirm the participants' eligibility status. If participants are required to make additional visits for screening (additional to normal care) reasonable travel expenses will be offered.

Full blood count and renal function will be assessed with other screening bloods.

Specific tests for screening include:

TSAT – all patients

Ferritin – all patients

NT-proBNP – stable outpatients

ECG (unless there are ECG results in the last 4 weeks prior to visit)

Formal screening for eligibility specific to the three settings, assuming the other inclusion and exclusion criteria (section 6) are met (clinical bloods taken in the last 4 weeks will be used if available):

1. **hospital in-patients**: *include if* :
   TSAT< 20% and/or ferritin <100ug/L *exclude if* :
   haemoglobin <9.0, or >13 g/dL in women or >14g/dL in men, or ferritin >400ug/L

2. **patients hospitalised in previous 6 months**: *include if* :
   TSAT< 20% and/or ferritin <100ug/L *exclude if* :
   haemoglobin <9.0, or >13 g/dL in women or >14g/dL in men, ferritin >400ug/L

3. **other patients attending out-patient clinics**: *include if* :
   TSAT< 20% and/or ferritin <100ug/L ***and*** NT-proBNP >250 ng/L in sinus rhythm or >1,000 ng/L in atrial fibrillation (or BNP of > 75 pg/mL or 300 pg/mL, respectively)
   exclude if : haemoglobin <9.0, or >13 g/dL in women or >14g/dL in men, or ferritin >400ug/L

7.1.3 Consent

Potential participants will be identified and screened by the clinical inclusion and exclusion criteria listed above. If patients fulfil clinical criteria, medical staff or appropriately trained support staff will seek consent for screening and participation in the trial from the patient. Following written consent, each signature will be dated by the signatory, the original retained in the site file, a copy provided to the patient and a copy inserted into the patient medical notes.

Data collected for routine clinical care will be used for clinical trial documentation (e.g. blood results, ECG). In the absence of routine blood results consent must be obtained prior to sampling of blood for study specific laboratory measurements.

Participants consenting for the study will also be invited to provide optional consent for long-term follow-up (maximum 10 years) of their electronic medical records. In sites participating in the biomarkers sub-study, participants will also be asked for optional consent for their blood samples to be stored for future analysis.

Sites will be required to scan and upload the consent forms into a secure study database for each consented patient.

7.1.4 Randomisation

Patients who are being randomised will be required to have undergone screening and have recent blood tests available from within the previous two weeks.

Study participants will be provided with a patient alert card, containing details of study participation, which they will be asked to carry at all times. Alert cards will be collected at the end of the patient's involvement in the study.

7.2 The Randomisation Scheme

Eligible and consenting patients will be randomised with equal probability to the two groups, with randomisation stratified by recruitment context (hospital inpatient/ hospitalisations for heart failure in the previous 6 months/ others recruited from out-patient clinics) and by study site using randomised permuted blocks of variable size to minimize predictability in this open study.

7.2.1 Method of implementing the allocation sequence

Randomisation will be achieved by accessing a web based randomisation system (with a telephone interactive voice response system as alternative). The investigator will provide the participant identifier and the system will check the participant's eligibility from information already entered in the eCRF and if appropriate the randomisation group will be allocated.

7.3 **Blinding** REMOVED FOR TRAINING

7.4 Baseline data

7.4.1 Demographics

- Date of birth
- Gender
- Ethnic group: white/black/Asian/other
- Smoking status: current/ex/never
- Recruitment status: hospitalised, hospitalisation within last 6 months, stable outpatient

7.4.2 **Medical history** DETAILS REMOVED FOR TRAINING

7.4.3 **Medication (snap shot of what patient is taking at that visit)** DETAILS REMOVED FOR TRAINING

7.4.4 Investigations

12 lead ECG (can use if one available within last 4 weeks):

AF/sinus rhythm
QRS duration (if >120 ms: left bundle branch block, right bundle branch block , interventricular conduction delay)
Paced (Y/N)

7.4.5 Baseline blood parameters (blood tests within 2 weeks can be used including screening bloods):

- Na, K, urea, creatinine, eGFR (MDRD)
- CRP
- Haemoglobin
- platelets
- MCV, MCHC, MCH, RDW
- TSAT
- Ferritin
- Bilirubin*
- Albumin*
- Random glucose*

*if available not mandated for the study

Prior to randomisation all patients require to have had blood results within the last two weeks.

Blood results for haemoglobin, TSAT and ferritin must be available prior to the dosing visit in the group assigned to the active treatment arm.

7.4.6 Personal identifiers (where permission has been given for record linkage to electronic medical records)

- Date of Birth
- Name
- Home address and postcode
- Unique identifier for medical record linkage (e.g. NHS number in England or Community Health Index (CHI) in Scotland, NHS number in Wales and the health and social care number in Northern Ireland)

All personal data will be encrypted in a separate study database that is not accessible to individuals working on the database containing the other trial data. All personal details will be managed according to ISO 27001:2013 compliant standard operating procedures.

7.4.7 Patient consent form

The signed patient consent form will be scanned into the study eCRF. This will facilitate remote monitoring of the patient's consent by study monitors who will be given secure access to view the consent forms.

All personal data will be encrypted in a separate study database that is not accessible to individuals working on the database containing the other trial data. All personal details will be managed according to ISO 27001:2013 compliant standard operating procedures.

7.5 Trial assessments

7.5.1 Baseline

Clinical and functional assessment

- systolic and diastolic blood pressure (after 5 minutes rest)
- heart rate and rhythm (after 5 minutes rest)
- height
- weight (clothed without coat and shoes)
- oedema (none, minor, moderate, severe)
- NYHA class (I-IV)
- ESA status to determine eligibility

Quality of life assessments

- EQ-5D
- Minnesota living with heart failure questionnaire

6 minute walk test

- Not mandated but encouraged. It is appreciated that not all participants will be able to perform this.

7.5.1.1 Infusion

Document dose of iron given. Participants randomised to the IV iron treatment group should discontinue use of oral iron while continuing to receive IV iron treatment.

7.5.1.2 Bloods for storage if recruited to sub-study

15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA and aprotonin. Blood will be centrifuged at 1500g for 20 mins at 4°C. Plasma will be siphoned, aliquoted and stored at -80° ± 10° until transport to the central laboratory on dry ice. At the time of analysis plasma samples will be defrosted at room temperature and analysed in a single batch.

7.5.2 Follow-up assessments

At each visit investigators should ensure that all participants be optimised according to current treatment guidelines; participants not optimised at baseline should be optimised soon after starting the study. Details of why they are not will be recorded.

Investigators should consider on an ongoing basis the cause of iron deficiency and the need for investigation according to guidelines and local practice. The protocol permits oral iron at the investigator's discretion in the standard practice arm. Investigation should be considered of participants with gastro-intestinal symptoms, very low or rapidly dropping ferritin, and those requiring very frequent dosing of IV iron (suggesting blood loss). All iron treatments, relevant investigations and non-serious adverse events of special interest (e.g. bleeds and transfusion requirement) will be recorded.

Women of childbearing potential (i.e. continuing menstrual cycle) will be asked about pregnancy status and contraceptive usage and a pregnancy test will be conducted (following informed consent). In this trial we will not recruit those wanting to become pregnant and will discontinue study treatment in women who become pregnant or who are on inadequate contraception. At each study visit women of

childbearing potential will be asked about their contraception status and a urine pregnancy test will be carried out for those getting IMP treatment. All women becoming pregnant will be withdrawn from study treatment. All pregnancies will be notified to the sponsor Pharmacovigilance Officer using the standard pregnancy notification form and the pregnancy followed to outcome*).*

7.5.2.1 Blood testing for all study visits following randomisation

Patients with chronic heart failure undergo regular blood testing for clinical management. Wherever possible we will use recent blood tests for the purposes of the study, and any blood tests taken for the study (except the samples for bio-bank) will be available to local clinicians involved in the care of the participants. The local research team will liaise with the clinical team (e.g. heart failure team, GP) where possible to ensure blood tests are coordinated for clinical and research use. It is anticipated that most participants will have the blood sample taken at the study visit. For those randomised to standard care this will mean that a single visit can be performed to obtain all the required data.

For participants randomised to IV iron it is anticipated that again most participants will have blood taken at the study visit. Those who do not meet the re-dosing criteria for IV iron will therefore only require a single visit. We *anticipate* that in the IV iron arm around half of participants will require re-dosing at visit 1 (i.e. at 4 weeks) and then further re-dosing would be required around once a year (i.e. approximately every third visit). Those participants who do require re-dosing will need to have a visit scheduled within 3 weeks of these blood tests results being available. At the infusion visit checks to ensure participant hasn't received iron or transfusion in the interim must be carried out. Overall around 5 out of 6 participants will require a single visit (from visit 2 onwards).

We acknowledge that some centres or specific patients may feel it is easier to get blood tests done prior to their study visit via standard local pathways (e.g. GP, hospital, community site, or heart failure team), generally having had the request initiated by the heart failure or research team. In order to use these results for the study these would need to be available within 3 weeks of study visits 2-13 and within 2 weeks of randomisation and study visit 1.

Participants can only be scheduled (and thereby receive) re-dosing if their blood tests have been entered into the eCRF.

7.5.2.2 4 week visit

An initial follow up will occur at 4 weeks following randomisation (+/- 2 weeks). The purpose of this visit is to ensure those patient receiving IV iron receive sufficient iron to correct underlying iron deficit.

The following will be documented/undertaken:

- Blood results must be available prior to the visit. Blood results within 2 weeks of the visit taken as per standard clinical pathways can be used. Results required: Creatinine, eGFR (MDRD) – all patients
- Haemoglobin – all patients
- TSAT – patients randomised to IV iron arm
- Ferritin – patients randomised to IV iron arm

These blood results must be entered in to the eCRF in advance of the infusion visit (if necessary) to ensure that the infusion can take place.

Medications

Clinical and functional assessment

- systolic and diastolic blood pressure (after 5 minutes rest)
- heart rate and rhythm (after 5 minutes rest)
- weight (clothed without coat and shoes)

- oedema (none, minor, moderate, severe)
- NYHA class (I-IV)
- if the patient is suffering from a significant ongoing infection as judged by the investigator infusion of IV iron (if required) should be postponed until the infection has passed or is controlled by antibiotics

Quality of life assessments

- EQ-5D

Serious adverse events

Study Iron Infusion

Document dose of iron given.

Events of Special Interest

Blood transfusions, including reasons: trauma, surgery, haemorrhage subcategorised as upper GI bleed, lower GI bleed, genitourinary (GU) bleed, other bleed and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss).

Haemorrhage classified by sites above and major if acute and requiring urgent transfusion and minor if not fulfilling these criteria.

7.5.2.3 4 monthly visits

All other planned follow up visits will happen every 4 months from randomisation with a window of +/- 2 weeks for each visit (i.e. 4*, 8, 12, 16, 20* months etc).

Blood results must be available prior to the visit. Blood results within 3 weeks of the visit taken as per standard clinical pathways can be used. Results required:

- Creatinine, eGFR (MDRD) – all patients
- Haemoglobin – all patients
- TSAT – patients randomised to IV iron arm
- Ferritin – patients randomised to IV iron arm

Blood results must be available prior to the dosing visit in the group assigned to the active treatment arm.

These blood results must be entered in to the eCRF in advance of the scheduled visit to ensure that the scheduled visit can take place as planned.

Medication

Clinical and functional assessment

- systolic and diastolic blood pressure (after 5 minutes rest)
- heart rate and rhythm (after 5 minutes rest)
- weight (clothed without coat and shoes)
- oedema (none, minor, moderate, severe)
- NYHA class (I-IV)
- if the patient is suffering from a significant ongoing infection as judged by the investigator infusion of IV iron (if required) should be postponed until the infection has passed or is controlled by antibiotics

Quality of life assessments
EQ-5D

Serious adverse events

Study Iron Infusion
Document dose of iron given.

Events of Special Interest
Blood transfusions, including reasons: trauma, surgery, haemorrhage subcategorized as upper GI bleed, lower GI bleed, GU bleed, other bleed and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss).
Haemorrhage classified by sites above and major if acute and requiring urgent transfusion and minor if not fulfilling these criteria.

7.5.2.4 Additional assessments at 4 month and 20 month visits:

Blood parameters (either taken at the visit or within the 3 weeks prior visit) must be available prior to the visit:

- Na, K, urea
- CRP
- platelets
- MCV, MCHC, MCH, RDW
- Bilirubin*
- Albumin*
- Random glucose*

*if available not mandated for the study

Quality of life assessments
Minnesota living with heart failure questionnaire

6 minute walk test
Not mandated but encouraged.

Bloods for storage if recruited to biomarkers sub-study

15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA and aprotonin. Blood will be centrifuged at 1500g for 20mins at 4°C. Plasma will be siphoned, aliquoted and stored at -80° ± 10°until transport to the central laboratory on dry ice. At the time of analysis plasma samples will be defrosted at room temperature and analysed in a single batch.

7.5.2.5 End of Study visit

LPLV is expected to be 4years and 4 months from first randomisation.

Medications

Clinical and functional assessment

- systolic and diastolic blood pressure (after 5 minutes rest)
- heart rate and rhythm (after 5 minutes rest)
- weight (clothed without coat and shoes)
- oedema (none, minor, moderate, severe)
- NYHA class (I-IV)

Quality of life assessments

- EQ-5D

Serious adverse events

Events of Special Interest

Blood transfusions, including reasons: trauma, surgery, haemorrhage subcategorised as upper GI bleed, lower GI bleed, genitourinary (GU) bleed, other bleed and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss).

Haemorrhage classified by sites above and major if acute and requiring urgent transfusion and minor if not fulfilling these criteria.

7.6 Retention and strategies for maximizing follow-up

Participants in the study have a significant medical condition and are expected to be good compliers with study procedures. Participants will be encouraged to attend all study visits. However, if they are unable or unwilling to attend all study visits they will be given an option of attending less frequently or only at the end of the study. Participants in the active treatment arm who miss study visits or who have irregular visit attendance should continue to be treated with IV iron if indicated according to the study blood tests and if the participant is willing to accept treatment.

Participants will be asked to provide consent to be contacted by telephone and for contact with their general practitioner or other health care provider to check on their current health status. As this is a morbidity/mortality study, follow-up for clinical events is critical. This will be maximised using record linkage to the participant's electronic medical records. No participant will be labelled as lost to follow-up. Participants will have the right to withdraw consent for further participation and for further data collection.

7.7 Treatment Interruptions and Withdrawal criteria REMOVED FOR TRAINING

7.8 Storage and analysis of samples SOME DETAILS REMOVED FOR TRAINING

7.8.1 Sample collection and processing

- Blood will be taken at baseline, 4 months and 20 months.

- Blood will be collected in pre-chilled sterilins containing EDTA and aprotonin, and centrifuged within 30 minutes at 1500g for 20mins at 4°C. Tubes for sample collection and storage will be sourced by each participating centre.
- Plasma will be separated, aliquoted and stored at -80° ± 10° at each centre.
- Individual patient samples will be identified with a unique, anonymised study number.

7.8.2 Sample transport to central laboratory and analysis

- Samples will ideally be transferred to the University of Leicester Department of Cardiovascular Sciences in a single batch at the end of recruitment to the study. More frequent transfer can be organised if there are local storage limitations.
- Samples will be transported on dry ice and stored at the central laboratory at -80° ± 10° until analysis. Transport by courier will coordinated by the Trial Manager.
- At the time of analysis individual aliquots will be defrosted at room temperature and analysed in a single batch for each biomarker of interest.
- Samples will be stored at -80° ± 10° in the central laboratory for possible future analysis for novel biomarkers.

7.9 End of trial

As this is a morbidity/mortality endpoint driven trial, the end of the trial will be defined by achievement of the desired number of primary outcomes or by a decision by the TSC and the Co-sponsors to stop the trial prematurely because of a recommendation from the IDMC or because of futility. Once it is anticipated that the desired number of primary endpoints will be achieved, end of study dates will be assigned to each participant. This will be done independently of randomised treatment group and of any study data.

8 TRIAL MEDICATION SOME DETAILS REMOVED FOR TRAINING

8.1 Name and description of investigational medicinal product(s)

Iron (III) isomaltoside 1000

Aqueous solution for injection/infusion contains 100mg/ml iron (as iron (III) isomaltoside 1000). Study sites will be provided with the following:

- 1 ml vials containing 100 mg iron as iron (III) isomaltoside 1000
- 5 ml vials containing 500 mg iron as iron (III) isomaltoside 1000
- 10 ml vials containing 1,000 mg iron as iron (III) isomaltoside 1000

8.2 Legal status of iron (III) isomaltoside 1000

8.3 Drug storage and supply

Study supplies must be stored in a locked, secure area with access limited to the Investigator and authorised site staff. Study supplies should be used as directed in the study protocol and not be supplied to any persons other than study participants. Drug will be distributed by Drug Company and must be stored at a temperature between 2°C and 30°C.

Investigational medicinal product (IMP) supplies will only be released to study sites by the sponsor once all the appropriate regulatory and governance approvals are in place. Further information on storage requirements and supply arrangements is provided in the study specific IMP Management and Accountability Manual.

8.4 Drug accountability requirements

The Investigator or designee must maintain accurate records of all study IMP movements for accountability purposes. They should include dates, quantities, batch numbers and expiry. Records must document adequately that:

- the patients were provided the doses specified by the protocol/amendment(s)
- all study drug provided was fully reconciled.

Unused study drug must not be discarded or used for any purpose other than the present study. Further information is provided in the study specific IMP Management and Accountability Manual.

8.5 Preparation and administration of iron (III) isomaltoside 1000

Drug is a dark brown, non transparent solution for injection/infusion. Each vial should be inspected prior to use for sediment or damage. Vials must be sediment-free and contain a homogenous solution. Vials are for single use only. Any unused solution must be discarded. Do not use vials after the expiry date.

To prepare the IV infusion, add the required dose to a maximum of 500ml sodium chloride 0.9%. Visually inspect the solution prior to infusion. The reconstituted solution must be clear and free from sediment. Do not infuse with another medicine or infusion fluid. The infusion should be administered via a sterile IV giving set. Supplies of sodium chloride 0.9% will be sourced from local hospital stock.

The rate of infusion is dependent on the dose as follows:

- Doses up to and including 1000mg must be infused over a minimum of 15 minutes
- Doses exceeding 1000 mg must be infused over a minimum of 30 minutes

Drug must be administered by appropriately trained staff who are able to evaluate and manage anaphylactic reactions. Full resuscitation facilities must be available at all times. Study participants must be carefully monitored for signs and symptoms of hypersensitivity reactions during and following each Drug dose. All patients must be observed for adverse effects for at least 30 minutes after the end of the infusion. Appendix 2 gives further details on patients who might be at higher risk of hypersensitivity reaction to IV iron and guidance on how reactions should be managed.

8.6 Dosage schedules

Haemoglobin, TSAT and ferritin levels must be available prior to dosing in the active treatment arm. All participants in the treatment arm will receive an infusion at the randomisation visit. If the participant is suffering from a significant ongoing infection as judged by the investigator, infusion of IV iron (if required) should be postponed until the infection has passed or is controlled by antibiotics. The dose administered is dependent on participant weight/haemoglobin level.

The participants will be reassessed 2-4 weeks after the first infusion, then at 4 months, and every 4 months thereafter during the trial. Patients will be eligible for dosing at the next planned study visit provided the TSAT remains <25% and/or ferritin <100ug/L; redosing will not take place if ferritin >400 ug/L.

Figure 1: Iron dosing schedule for initial infusion and subsequent infusions according to haemoglobin and weight. (Subsequent infusion will only be administered provided the TSAT remains <25% and/or ferritin <100ug/L; redosing will not take place if ferritin >400 ug/L.)

Iron to be administered as iron (III) isomaltoside 1000.

Haemoglobin	Body weight < 50 kg	Body weight 50 to <70 kg	Body weight ≥ 70 kg
≥10 g/dL	20mg/kg	1000 mg	20mg/kg up to a maximum of 1500 mg
<10 g/dL	20mg/kg	20mg/kg	20mg/kg up to a maximum of 2000 mg

Doses will be rounded down to the nearest 100mg.

8.7 Dosage modifications

8.8 Known drug reactions and interaction with other therapies

8.9 Concomitant medication

8.10 Trial restrictions

8.11 Assessment of compliance

Treatment compliance will be assessed by recording the IV dosing regimen as per the assigned treatment group in all participants during the course of this trial. Iron isomaltoside 1000 will be administered by health care professionals who will record the amount of drug administered to the participant in the eCRF.

8.12 Name and description of each Non-Investigational Medicinal Product (NIMP)

There are no Non-Investigational Medicinal Products identified for this trial.

9 PHARMACOVIGILANCE SOME DETAILS REMOVED FOR TRAINING

9.1 Definitions

9.2 Operational definitions for (S)AEs

9.3 Recording and reporting of AEs, Events of Special Interest, SAEs AND SUSARs

All AEs occurring during the trial that are observed by the Investigator or reported by the participant will be recorded in the participant's medical records whether or not attributed to trial medication. All Events of Special Interest will be recorded in the participant's medical records and on the eCRF.

AEs will be recorded from consent until the later of 30 days post cessation of trial treatment or the end of the study.

Serious Adverse Events (SAE)

SAEs will be recorded and reported (as appropriate) to the sponsor from randomisation until the later of 30 days post cessation of trial treatment or the end of the study.

Full details of SAEs will be recorded in the electronic Case Report Form.

Any change of condition or other follow-up information should be added to the eCRF and forwarded to the Sponsor (if reportable SAE) as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Assessment of Adverse Events

Recording and reporting of SAEs

All SAEs arising during the clinical trial will be recorded in the eCRF soon as reasonably practicable and in any event within 24hours of first becoming aware of the event. Any follow-up information should also be reported.

If recording in the eCRF is not possible a paper SAE form should be completed:

1. The SAE form is downloaded from www.glasgowctu.org, printed off, completed and signed. The form is then faxed to the Glasgow Clinical Trials Unit Pharmacovigilance (PV) Office on +44(0)141 357 5588. If faxing is not possible a copy of the SAE form should be scanned and emailed to: pharmacovig@glasgowctu.org. If this website is unavailable a paper copy of the SAE form is filed in the Investigator Site File at each site.
2. If necessary a verbal report can be given by contacting the PV Office on +44(0)141 330 4744. This must be followed up as soon as possible with an electronic or written report.

Reporting to sponsor

All SAEs, other than those documented in 9.2 above as excluded from immediate reporting to the sponsor, will be reported to the sponsor's PV office.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor will inform the MHRA and the REC of SUSARs within the required expedited reporting timescales:

- **Fatal or life threatening SUSARs**: not later than 7 days after the sponsor had information that the case fulfilled the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.

- **All other SUSARs**: not later than 15 days after the sponsor had information that the case fulfilled the criteria for a SUSAR

The sponsor will report SUSARs to the MHRA via the MHRA eSUSAR reporting system and to REC by email with accompanying CTIMP Safety Report Form.

9.4 Responsibilities for Safety Reporting and Review

This section details the responsibilities for reporting and reviewing safety information arising from the trial.

Principal Investigator (PI):

1. Checking for AEs and ARs when participants attend for treatment / follow-up.
2. Ensuring that AEs are recorded and reported in line with the requirements of the protocol.
3. Ensuring that all SAEs are recorded and appropriate SAEs reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

4. Using medical judgement in assigning seriousness, causality, severity and expectedness with reference to the trial protocol and Reference Safety Information.
5. Using definitions in this protocol, flag events of special interest or potential endpoints

Chief Investigator (CI)

Sponsor:

Trial Steering Committee:

Independent Data Monitoring Committee:

Clinical Endpoint Committee (CEC):

9.5 Pregnancy reporting

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE and must be reported as per SAE reporting procedure above.

Any **pregnancy** occurring in a female trial participant or female partner of a male trial participant who becomes pregnant while participating in the Trial will be reported by the PI (or designee) to the Chief Investigator and the sponsor using the sponsor Pregnancy Reporting Form (available at http://www.glasgowctu.org/complete-paper-sae.aspx within two weeks of the PI first becoming aware of the pregnancy.

The trial participant will also be followed up to determine the outcome of the pregnancy and follow-up information forwarded to the PV office. Any resulting SAEs should be reported as per SAE reporting procedure above.

9.6 Overdose

However any overdose of the IMP should be documented as a protocol deviation and reported to the sponsor.

If an SAE is associated with an overdose ensure that the overdose if fully described in the SAE report form.

9.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor will phone the MHRA's Clinical Trial Unit on 020 3080 6456, ideally within 24 hours. This will be followed up no later than 3 days from the date the measures are taken, giving written notice to the MHRA (who will advise the format required) and the relevant REC of the measures taken and the circumstances giving rise to those measures. A substantial amendment must also be submitted to the MHRA.

9.8 The type and duration of the follow-up of participants after adverse events.

Adverse events and reactions will be recorded, reported and followed up in line with this protocol until study completion or for a minimum of 30 days after participant's last dose of the IMP, whichever is later.

Any SUSAR identified will be reported to the Sponsor and to the Regulatory Authorities irrespective of how long after IMP administration the reaction has occurred.

9.9 Development safety update reports

10 STATISTICS AND DATA ANALYSIS SOME DETAILS REMOVED FOR TRAINING

10.2 Anticipated recruitment rate

We intend to recruit from approximately 50 secondary care centres. These will be high volume Heart failure centres (for example submitting >20 patients per month to the National Heart Failure audit) with an established research infra-structure. We anticipate that patients will be recruited in approximately the following proportions:

(i) 50% in-patients
(ii) 30% with hospitalisation in previous 6 months
(iii) 20% from out-patient clinics with elevated NT-proBNP

10.3 Statistical analysis

10.4 Subgroup analyses

10.5 Interim analysis and criteria for the premature termination of the trial

10.6 Subject population

10.7 Procedure(s) to account for missing or spurious data

10.8 Other statistical considerations.

10.9 Economic evaluation

11 DATA HANDLING SOME DETAILS REMOVED FOR TRAINING

11.1 Source Documentation

11.2 Data collection

An eCRF, developed by the Robertson Centre for Biostatistics, will capture all data required to meet this protocol's requirements. Access to the eCRF will be restricted, via a study-specific web portal, and only authorised site-specific personnel will be able to make entries to their patients' data via the web portal. The Investigator, or his/her designee will be responsible for all entries into the eCRF and will confirm that the data are accurate, complete and verifiable. Data will be stored in a MS SQL Server database.

Paper worksheets which represent the eCRF content will be available to facilitate data capture at the study sites.

Direct access to the web portal will be granted, on request, to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.3 Data Validation

Where it is practical, data will be validated at the point of entry into the eCRF. Any additional data discrepancies will be flagged to the investigator and any data changes will be recorded to maintain a complete audit trail (reason for change, date change made, who made change).

11.4 Data Security

The Robertson Centre for Biostatistics systems are fully validated in accordance with industry and regulatory standards, and incorporate controlled access security. High volume servers are firewall protected and preventative system maintenance policies are in place to ensure no loss of service or data. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. Data are backed up on-site nightly and off-site to a commercial data vault weekly. The Robertson Centre for Biostatistics has an ISO 9001:2008 quality management system and ISO 27001:2013 for Information Security, and is regularly inspected against the standards by the British Standards Institution.

11.5 Archiving

The Trial Master File will be archived by the Co-Sponsors at the end of the trial for a minimum period of five years.

Archiving of Site Files will also be for a minimum of five years form completion of the trial, and this action will be delegated to the sites in the Clinical Trial Site Agreement that will be put in place between Co-Sponsors and Sites. Sites will be notified by the Co-Sponsors when Site files can be archived.

Destruction of site files can only take place with the approval of the Co-Sponsors.

12 MONITORING, AUDIT & INSPECTION

Monitoring will be conducted by XXX Monitor (s) in accordance with local Standard Operating Procedures. The level, frequency and priorities of monitoring will be based on the outcome of the completed risk assessment, and will be clearly documented in the Monitoring Plan which will be approved by the XXX Research Governance Manager.

13 ETHICAL AND REGULATORY CONSIDERATIONS SOME DETAILS REMOVED FOR TRAINING

13.1 Research Ethics Committee (REC) review & reports

13.2 Peer review

13.3 Public and Patient Involvement

13.4 Regulatory Compliance

13.5 Protocol compliance

13.6 Notification of Serious Breaches to GCP and/or the protocol

13.7 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

- Personal information will be collected via the eCRF to enable record linkage to be carried out and to provide electronic access to study monitors to a copy of the signed informed consent document. These data items will be encrypted and only those individuals who require to see these data i.e. the person performing the record linkage and site research team staff or the study monitor, as appropriate, will be able to view them. All electronic data will be held

securely in accordance with ISO 27001:2013 at the Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit. All Centre staff are required to sign confidentiality agreements and to follow Standard Operating Procedures in accordance with Good Clinical Practice and ISO certification.

- The trial data managers, statisticians, health economists or any other staff who will perform data related tasks will only be able to access depersonalised data where the participant's identifying information is replaced by a unique study identifier.
- Only those that have been trained and approved will be able to enter or view any data via the web portal. Each site can only see their own patients' data. Patient consent forms will be stored at the study site in a secure location accessible only to study teams.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

13.9 Indemnity

The Co-Sponsors will ensure that provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial in accordance with Part 2 (14) of Schedule 1 to SI 2004/1031.

13.10 Amendments

13.11 Post trial care

At the end of the trial, participants will be returned to usual care as defined by local and national guidelines at that time. The results of the trial may of course have an impact on these guidelines and the future care of patients with heart failure.

13.12 Access to the final trial dataset

14 DISSEMINATION POLICY DETAILS REMOVED FOR TRAINING

15 **REFERENCES** DETAILS REMOVED FOR TRAINING

16. APPENDICES

16.1 Appendix 1 – Risk

Risks associated with trial interventions ☐ LOW ≡ Comparable to the risk of standard medical care ☒ MODERATE ≡ Somewhat higher than the risk of standard medical care ☐ HIGH ≡ Markedly higher than the risk of standard medical care
Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given): All patients are monitored with ferritin/TSAT to avoid iron overload.

<table>
<tr><td colspan="5">An IDMC will be convened to monitor all SAEs.

Risks and mitigations associated with the intervention are outlined in more detail in the Protocol section 2.1.

Co-Sponsors will also carry out a detailed risk assessment of all aspects of the study as part of the approval process (SOP 04.013)</td></tr>
<tr><td colspan="2">What are the key risks related to therapeutic interventions you plan to monitor in this trial?</td><td colspan="3">How will these risks be minimised?</td></tr>
<tr><td>IMP/Intervention</td><td>Body system/Hazard</td><td>Activity</td><td>Frequency</td><td>Comments</td></tr>
<tr><td>IV administration of Iron-maltoside-1000</td><td>Immune:

Hypersensitivity/an a-phylactic reactions</td><td>Cardio-pulmonary resuscitation equipment available at site where administered

Patients with known hypersensitivity to any iron preparation, or have a contra-indication to the IMP according to the SmPC will not be recruited to the study</td><td>Rare</td><td></td></tr>
<tr><td></td><td>Increased risk of infection/oxidative stress</td><td>IDMC will specifically receive and review information on infection – related hospitalisations</td><td>Rare</td><td></td></tr>
<tr><td>Others?</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="5">Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

See above</td></tr>
</table>

16.2 Appendix 2 – A guide for managing hypersensitivity reactions which occur during administration of Intravenous (IV) iron

16.3 Appendix 3: Contraception

16.4 Appendix 4 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA

IRAS Form

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

(●) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Is this a commercially sponsored Phase 1 or Phase 1/2a trial involving healthy volunteers?

( ) Yes (●) No

2b. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2c. Please answer the following question:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA? ○ Yes ◉ No

2d. Please answer the following question:

Is this a trial of a gene therapy medicinal product? ○ Yes ◉ No

2e. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ○ Yes ◉ No

b) Will you be taking new human tissue samples (or other human biological samples)? ◉ Yes ○ No

c) Will you be using existing human tissue samples (or other human biological samples)? ○ Yes ◉ No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ○ England
- ◉ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which review bodies are you applying to?

- ☐ HRA Approval
- ☑ NHS/HSC Research and Development offices
- ☐ Social Care Research Ethics Committee
- ☑ Research Ethics Committee
- ☑ Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines
- ☐ Gene Therapy Advisory Committee (GTAC)
- ☐ Confidentiality Advisory Group (CAG)
- ☐ National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Clinical trial of an investigational medicinal product

NHS/HSC R&D Form (project information)

Please refer to the Submission and Checklist tabs for instructions on submitting R&D applications.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

A3-2. National coordinating investigator (for a multicentre trial) **or principal investigator** (for a single centre trial)

◉ National coordinating investigator
○ Principal investigator

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

Title Forename/Initials Surname

Address

Post Code
E-mail
Telephone
Fax

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):
Sponsor's/protocol number:
Protocol Version:
Protocol Date:
Funder's reference number:
Project website:

Registry reference number(s):
The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov Identifier (NCT number):
European Clinical Trials Database (EudraCT) number:

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

◯ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Chronic heart failure (CHF) is a very common medical problem. Despite improvements in treatment, many patients suffer limiting symptoms of shortness of breath and fatigue. Hospitalisation for CHF is common and life expectancy reduced. Many patients with CHF have a deficiency of iron (low iron levels or cannot use iron properly), and this is associated with poorer outcomes. Some small research studies have suggested that giving patients intravenous iron improves symptoms in the short term. It is unknown, however, whether correcting iron deficiency is beneficial to patients with CHF in the long term and whether it improves life expectancy and keeps them out of hospital. This study will help us answer these key questions.
This study will address whether the additional use of Intravenous (IV) iron on top of standard care will improve the out look for patients with heart failure and iron deficiency. One group of participants will receive treatment with iron injections and the other group will not receive any iron injections.
The study will take place in about 50 secondary care sites (hospitals) across the UK.
Participants will be recruited over a period of two years and will be followed up for a minimum of two and a half years (average duration of three years per participant). After the initial visits, participants will be seen every four months.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

In current clinical practice if iron deficiency is detected, patients may receive no treatment, oral or IV iron. Although historically IV iron administration was associated with a relatively high rate of serious adverse events, this was largely due to allergenic high molecular weight iron dextran preparations. Newer preparations, including Iron isomaltoside 1000, rarely cause hypersensitivity or anaphylactic reactions. Other reactions that are thought to have a non-allergic basis ('labile iron' reactions) are also uncommon and rarely serious. However, as with all IV iron preparations, cardio-pulmonary resuscitation equipment should be available at the site of administration. A recent European Medicines Agency report recommended that IV iron should not be given to patients with known serious hypersensitivity to any iron preparation, and therefore these patients are excluded from the trial. Patients with a documented contra-indication to iron isomaltoside 1000 according to the Summary of Product Characteristics (SmPC) will not be included in the study. There is a theoretical possibility that IV iron may increase the risk of infection and cause oxidative stress. The independent data monitoring committee (IDMC) will review all serious adverse events with careful attention to infection-related hospitalisations as well as cardiovascular (CV) events. Appendix 2 in the Study Protocol gives further details on patients who might be at higher risk of hypersensitivity reaction to IV iron and guidance on how reactions should be managed.

Iron isomaltoside 1000 is approved for treatment of iron deficiency. The current study will include some patients without anaemia (limited to haemoglobin <13g/dL in females and <14g/dL in males) since previous studies have suggested benefit of IV iron irrespective of the presence of anaemia in iron deficient patients with CHF. Patients are monitored to avoid iron overload.

For all IV iron products the risk of hypersensitivity reactions is enhanced for patients with known allergies including drug allergies, and those patients with a history of severe asthma, eczema or other atopic allergies. There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis). Since the hypothesis underlying the study is that patients with CHF will derive a significant benefit from IV iron treatment relating to cardiovascular mortality and heart failure hospitalisation the investigators believe that the potential benefit of treatment outweighs any additional risk in these subject groups and therefore they should not be excluded from potential benefit. As already described, all participants will be carefully monitored during IV iron infusion and for a minimum of 30 minutes after completion for any adverse reaction including hypersensitivity reactions and anaphylaxis. Resuscitation equipment will be available during all IV iron infusions. The final decision to include a participant who might be at higher risk will be based upon investigator judgement.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A8. Type of medicinal trial:

- ☐ Clinical trial of an unlicensed investigational medicinal product
- ☑ Clinical trial of a licensed medicinal product in new conditions of use (different from those in the SmPC, i.e. new target population, new dosage schemes, new administration route, etc.)
- ☐ Clinical trial of a licensed medicinal product used according to the SmPC
- ☐ Other (please specify)

A9. Phase of medicinal trial: *(Tick one category only)*

Human pharmacology (Phase I)	○ Yes	◉ No
Therapeutic exploratory trial (Phase II)	○ Yes	◉ No
Therapeutic confirmatory trial (Phase III)	○ Yes	◉ No
Therapeutic use trial (Phase IV)	◉ Yes	○ No

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To establish in patients with chronic heart failure and iron deficiency whether treatment with intravenous iron is effective in reducing death due to cardiovascular problems, and hospitalisation due to heart failure.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

We will also determine whether intravenous iron is safe, improves quality of life and is cost effective.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

Sample size.
The anticipated primary endpoint rate in the control group is 30% in the first year and 60% by three years (median follow-up). Sample size calculations based on recurrent event analyses are complex. Therefore, conservatively, we have based them on a time to first event analysis using the Wald statistic in a Cox proportional hazards model. We estimate that 570 patients per group (yielding 631 first events) will provide 80% power to detect a hazard ratio of 0.8 (20% reduction in hazard which we believe is a clinically meaningful effect). All analyses will be conducted on an intention to treat basis. We anticipate an incomplete follow up of <1% by using national record linkage. To allow for loss of information due to non-CV mortality and potential deviation from assigned therapy during the trial, we intend to recruit 650 patients per group.

Recruitment.
We intend to recruit from approximately 50 secondary care centres in the UK. These will be high volume heart failure centres with an established research infra-structure. We anticipate that patients will be recruited in the following proportions:
(i) 50% in-patients
(ii) 30% with hospitalisation in previous 6 months
(iii) 20% from out-patient clinics with elevated NT-proBNP

There are no large trials currently recruiting patients with left ventricular ejection fraction <45% or evaluating IV iron on heart failure hospitalisation and mortality in patients wilth chronic heart failure in the UK. We expect that participants will be recruited over two years with a ramp-up of recruitment in the first 6 months and uniformly thereafter.

Participants will be identified by secondary care sites during or after hospitalisation (this will include local datasets), from outpatients and other local heart failure pathways (including community services). The precise set-up of these heart failure services/pathways will vary according to locality. Patients will be identified by a number of potential

pathways:
1. In-patients with hospitalisation for heart failure
2. heart failure hospitalisation within the last 6 months
3. stable CHF patients identified in out-patient clinics/ heart failure services.

Patients with a diagnosis of heart failure will be pre-screened based on recent documentation of left ventricular ejection fraction (LVEF). Only patients with LVEF documented as <45% within 6 months will be approached to consider consenting to undergo formal screening and possible participation in the study.

It is anticipated that the majority of patients will be identified by the heart failure team (for example doctors, specialist heart failure nurses, heart failure pharmacists) directly involved in the care of the patients (including secondary care sites for both in and outpatients and community services). Patients may be under the care of different clinical teams. The initial approach to the patient will by the clinical team who are directly involved in their clinical care and permission sought to pass on their details to the research team (the research team will on occasions also be the clinical team).

Likely response rates.
Feedback from patients during the protocol development was positive and suggestions assimilated. It was felt that there was a high likelihood of recruiting and retaining patients in the study. The study is designed to be inclusive and reflect clinical practice. There is no upper age limit; hospitalised patients can be randomised and receive IV iron shortly before discharge; heart failure medications do no have to be fully optimised before randomisation i.e. iron is give in parallel to changes in other treatments as required as part of standard clinical care.

Data from the Hull out-patient heart failure services show that the prevalence of iron deficiency is higher in patients with borderline or low haemoglobin. Accordingly, screening will be resticted to patients with haemoglobin less than or equal to 1 g/dL above the World Health Organisation's definition of anaemia, amongst whom iron deficiency will be present in about half. Amongst patients hospitalised for heart failure in West Middlesex and Portsmouth data show that about 50% are iron deficient.

Considering Portsmouth NHS Trust alone the Chief Investigator has shown that: (i) of 300 patients submitted to the National Heart Failure Audit in 2013 from cardiology wards alone, 65% had a LVEF <45% of whom half had iron deficiency, (ii) a prospective observational study (IRONSTATS) of patients hospitalised with heart failure could identify about 20 patients per month and consent about six of these. Our consent rate may be influenced, for better or worse, by the interventional nature of the study and longer follow up. We estimate that ~20% of hospitalised patients who fulfil inclusion criteria will consent. For Portsmouth this would equate to 1-2 patients per month from this route alone. It is acknowledged that for some centres this will be lower.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [x] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
The study has been developed following consultation with patient groups and an independent community heart failure service. Feedback was positive and suggestions assimilated. Full endorsement was given to the need for the study. Patients felt there was a high likelihood of recruiting and retaining participants in the study. The trial steering committee, which provides overall supervision of the trial, has a patient representative on it.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [x] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

1. Age ≥18 years
2. LVEF <45% within the last 6 months using any conventional imaging modality
3. New York Heart Association (NYHA) class II – IV
4. Iron deficient - defined as a TSAT<20% and/or ferritin >100ug/L
5. Evidence of being in a higher risk heart failure group:
a. Current (with intention to discharge in next 48 hours) or recent (within 6 months) hospitalisation for heart failure, or
b. Out-patients with NT-proBNP >250 ng/L in sinus rhythm or >1,000 ng/L in atrial fibrillation (or BNP of > 75 pg/mL or 300 pg/mL, respectively)
6. Able and willing to provide informed consent

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

1. Haematological criteria: ferritin >400ug/L; haemoglobin <9.0 or >13 g/dL in women or >14g/dL in men; (B12 or folate deficiency should be corrected but do not exclude the patient)
2. MDRD estimated glomerular filtration rate (eGFR) <15ml/min/1.73m2
3. Chronic defined need for IV iron therapy
4. Likely to need or already receiving erythropoiesis stimulating agents (ESA)

5. Planned cardiac surgery or revascularisation or cardiac device implantation; within 3 months of a primary diagnosis of type 1 myocardial infarction (excluding small troponin elevations in the context of heart failure admissions), cerebrovascular accident (CVA), major CV surgery or percutaneous coronary intervention (PCI), cardiac device implantation or blood transfusion; on active cardiac transplant list; left ventricular assist device implanted
6. Any of the following comorbidities: active infection (if the patient is suffering from a significant ongoing infection as judged by the investigator recruitment should be postponed until the infection has passed or is controlled by antibiotics), other disease with life expectancy of <2 years, active clinically relevant bleeding in the investigators opinion, known or suspected gastro-intestinal malignancy
7. Pregnancy or women of childbearing potential (i.e. continuing menstrual cycle) not using effective contraception – see Appendix 3 of the protocol
8. Contra-indication to IV iron in the investigator's opinion according to current approved Summary of Product Characteristics: hypersensitivity to the active substance, to Monofer® or any of its excipients (water for injections, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment)); known serious hypersensitivity to other parenteral iron products; non-iron deficiency anaemia (e.g. haemolytic anaemia); iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis); decompensated liver cirrhosis and hepatitis
9. Participation in another intervention study involving a drug or device within the past 90 days (co-enrolment in observational studies is permitted)

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Informed consent process and discussion	1	0	As long as required	Completed by study doctors (or delegated support staff with appropriate training) at study site.
Confirming inclusion/exclusion criteria (screening and randomisation)	2	0	15 mins	Completed by study doctors at study site.
Demograhics/medical/surgical history/prior medications	1	0	30 mins	Completed by study doctors or study nurses at study site.
Concomitant medications (this may be fewer depending on the point in the recruitment timeline that the participant is consented into the study)	14	0	5 mins	Completed by study doctors or study nurses at study site.
Inquiry regarding potential adverse events (this may be fewer depending on the point in the recruitment timeline that the participant is consented into the study)	15	0	10 mins	Completed by study doctors or study nurses at study site.
Inquiry regarding Infusion reaction (only those in active treatment arm) (this may be fewer depending on the point in the recruitment timeline that the participant is consented into the study)	15	0	5 mins	Completed by study doctors or study nurses at study site.
Minnesota Questionnaire	3	0	10 mins	Completed by the patient under supervision of the study nurses at the study site.
EQ5D questionnaire (this may be fewer depending on the point in the recruitment timeline that the participant is consented into the study)	15	0	5 mins	Completed by the patient under supervision of the study nurses at the study site.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Blood sample for screening: TSAT, ferritin, creatinine, eGFR and haemoglobin	1	0	5 mins	Completed by study doctors or study nurses at study site.
Blood sample for screening with NT-BNP (only for patients recruited from out-patient services)	1	0	5 mins	Completed by study doctors or study nurses at study site.
Blood sample for creatinine, eGFR and haemoglobin (this may be fewer depending on the point in the recruitment timeline that the participant is consented into the study)	14	14	5 mins	Completed by study doctors or study nurses at study site. When available within protocol defined time limits use local lab blood results (standard clinical practice).
Blood sample for TSAT and ferritin treatment arm only (NB these are additional test requests on blood samples taken for routine clinical practice) (this may be fewer as above)	13	0	5 mins	Completed by study doctors or study nurses at study site
Blood sample for MCV, MCHC, MCH, RDW, Platelets, Sodium, Potassium, Urea, CRP (NB these are available tests from blood samples taken for routine clinical practice)	3	3	5 mins	Completed by study doctors or study nurses at study site. When available within protocol defined time limits use local lab blood results (standard clinical practice).
Blood sample for Bilirubin, Albumin, Random Glucose (NB these will be documented if available from blood samples taken for routine clinical practice at baseline, 4 and 20 months)	3	3	5 mins	Results to be collected from local lab if taken as part of standard clinical practice within protcol defined limits.
Study drug administration: treatment arm only NB we anticipate that after the first infusion, participants will require a further infusion around every 3rd visit (this may be fewer)	5	0	45-60 mins	Completed by study doctors or study nurses at study site. (includes 30min observation post infusion)
Clinical assessment of heart failure signs and symptoms including blood pressure and heart rate (this may be fewer)	16	0	15 mins	Completed by study doctors or study nurses at study site.
Weight (this may be fewer depending on the point in the recruitment timeline that the participant is consented into the study)	16	0	2 mins	Completed by study doctors or study nurses at study site.
Height	1	0	2 mins	Completed by study doctors or study nurses at study site.
6 Minute walk test	3	0	10 mins	Completed by study doctors or study nurses at study site. Not mandated but encouraged.
Electrocardiography (ECG)	1	0	10 mins	Completed by study doctors or study nurses at study site.
Biomarker substudy (only for participants who have consented to this)	3	0	5 mins	Completed by study doctors or study nurses at study site.

Pregnancy test (NB for women of child bearing potential and receiving the IV iron)	5	0	5 mins	Completed by study doctors or study nurses at study site.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

Average of 3 years (event driven trial, expected maximum 4 and a half years, minimum 2 and a half years – anticipated 2 years recruitment and a projected further 2 years of treatment/assessments, and a further closeout visit giving a range of projected patient participation of 2.5–4.5 years).

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

1. Blood tests - participants with chronic heart failure should have regular blood tests to monitor their condition. According to national guidelines this is a minimum of twice a year and in light of the severity of heart failure of participants recruited to this study, the investigators feel as though it should be a minimum of three times a year. As such wherever possible clinically indicated blood tests will be performed at the same time as research blood tests required for this study.

2. Frequency of visits - whilst the investigators have tried to keep the number of study visits to a minimum (three times per year after initial and 4 week visits), there may be some participants who view this as inconvenient.

3. Iron infusion and reactions - as previously mentioned, infusions of iron may cause hypersensitivity reactions in some participants (see appendix 2 of the protocol). This can include pain and discomfort. All participants receiving the IV iron will be carefully monitored for the duration of infusion and for a minimum of 30 minutes after the treatment.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

The participant may feel better and experience less breathlessness and fatigue. There will potentially be fewer hospital admissions and a reduction in the number of cardiovascular deaths. There is no guarentee that the participant will benefit in any way. Nevertheless, results from this study may provide information which will help us to treat heart failure patients with iron deficiency more appropriately in the future.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

At the moment, there is no clear guidance on using intravenous iron in the treatment of iron deficiency in heart failure patients. Therefore, once the study has been completed, the participant's responsible physician will discuss the best treatment option dependent on the outcome of the study. This may be the same treatment as used prior to study entry.

A26. What are the potential risks for the researchers themselves? *(if any)*

There are no foreseeable risks to the researchers.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Patients will be identified by a number of potential pathways:
1. In-patients with hospitalisation for heart failure
2. heart failure hospitalisation within the last 6 months
3. stable CHF patients identified in out-patient clinics/ heart failure services.

Patients with a diagnosis of heart failure will be pre-screened based on recent documentation of left ventricular ejection fraction (LVEF). Only patients with LVEF documented as <45% within 6 months will be approached to consider consenting to undergo formal screening and possible participation in the study.

It is anticipated that the majority of patients will be identified by the heart failure team (for example doctors, specialist heart failure nurses, heart failure pharmacists) directly involved in the care of the patients (including secondary care sites for both in and outpatients and community services). Patients may be under the care of different clinical teams. The initial approach to the patient will be by the clinical team who are directly involved in their clinical care and permission sought to pass on their details to the research team (the research team will on occasions also be the clinical team).

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

(●) Yes ( ) No

Please give details below:
Potential participants may also be identified from local heart failure databases by the clinical and/or heart failure team. Initial contact with patients will be by the clinical and/or heart failure team to seek permission to pass on details to the research team.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Potential participants will only be identified by the clinical and/or heart failure team who are involved in their care. Any local resources used to identify participants will already be in use and subject to standard NHS procedures regarding confidentiality.

Participants consenting for the study will also be invited to provide optional consent for long-term follow-up (maximum 10 years) of their electronic medical records. This consent includes permission to collect identifiable information that will be used to perform record linkage. This information will be encrypted and stored separately from other clinical research data and will not be accessible by individuals working on the clinical database.

Participants will be asked to consent to allow their consent forms to be scanned and uploaded to a central secure database to facilitate remote monitoring.

Participants' clinical research data will be stored in the study database and will be identified only by a unique subject number.

All electronic data will be held securely in accordance with ISO 27001:2013 at the Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit. All Centre staff are required to sign confidentiality agreements and to follow

Standard Operating Procedures (SOPs) in accordance with Good Clinical Practice and ISO certification for information security.

All site staff will be given training on information security aspects of the study. Data centre web servers are secured by digital certificates. This ensures all data being transferred to these servers are encrypted. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. The Robertson Centre for Biostatistics has an ISO 9001:2008 quality management system and ISO 27001:2013 for Information Security, and is regularly inspected against the standards by the British Standards Institution. Centre staff are all trained in information security SOPs and sign confidentiality agreements.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

○ Yes ◉ No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

◉ Yes ○ No

If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).

Posters will be used in local hospitals, see attachment.

A29. How and by whom will potential participants first be approached?

Participants will be approached by a member of the clinical or heart failure team directly involved with their clinical care. This will be in person or using the approved patient invitation letter and patient information sheet.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

The potential participant will be provided with verbal information about the study and the approved patient information sheet (PIS) and given a minimum of 24 hours to make a decision. The medical staff or delegated support staff (with appropriate training in GCP, informed consent and the protocol) will then obtain the consent after informed discussion with the participant.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

A minimum of 24 hours.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- (•) Yes
- ( ) No
- ( ) Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

We will permit inclusion of participants who have been recruited to another intervention study involving another drug or device providing their involvement in that study has been completed for more than 90 days prior to randomisation. Co-enrolment in observational studies is permitted.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters)*

Participants who need an interpreter for their clinical consultation would use the same service to facilitate explanation of the study if approached in person. No special arrangements have been made to translate the written information for patients, although this can be addressed if required at a local level.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

Welsh language copies of key study documents (i.e. patient information sheets and informed consent forms) will be made available if requested.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

If significant information relevant to their continued participation becomes available we will discuss this with them at their next study visit. If necessary the research team will phone and/or write to participants between study visits. We will ask participants when they enter the study how they wish to be contacted.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- [x] Access to medical records by those outside the direct healthcare team
- [ ] Access to social care records by those outside the direct social care team
- [x] Electronic transfer by magnetic or optical media, email or computer networks
- [x] Sharing of personal data with other organisations
- [ ] Export of personal data outside the EEA
- [x] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [ ] Storage of personal data on any of the following:

- [x] Manual files (includes paper or film)
- [x] NHS computers
- [ ] Social Care Service computers
- [ ] Home or other personal computers
- [x] University computers
- [ ] Private company computers
- [ ] Laptop computers

Further details:

A37. Please describe the physical security arrangements for storage of personal data during the study?

Personal information held at study sites must be stored in lockable filing cabinets and in accordance with local trust procedure.

Personal information held at the study data centre, Robertson Centre for Biostatistics, University of Glasgow could be held on paper, on live study databases and on database back up media. The centre is physically secured by controlled access, covered by security cameras. All paper based information will be stored in lockable filing cabinets. Study database servers are housed in a secure server room and study database back ups are held locally in lockable fireproof cabinets and off site in a secure commercial data vault (Iron Mountain).

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

All site staff will be given training on information security aspects of the study. Data centre web servers are secured by digital certificates. This ensures all data being transferred to these servers are encrypted. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. The Robertson Centre for Biostatistics has an ISO 9001:2008 quality management system and ISO 27001:2013 for Information Security, and is regularly inspected against the standards by the British Standards Institution. Centre staff are all trained in information security SOPs and sign confidentiality agreements.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Participants consenting for the study will asked to provide consent for access to relevant sections of their medical notes and for data collected during the study to be looked at by individuals from the study team, from regulatory authorities and from or their appointees. This consent includes permission to collect identifiable information.

Participants' clinical research data will be accessed by staff in the data centre to perform data management and statistical analyses.

Endpoint adjudication committee will have access to individual case summaries and related source documents.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data will be stored in the Robertson Centre for Biostatistics and will be analysed by statisticians who are employees of the Centre.

A42. Who will have control of and act as the custodian for the data generated by the study?

Title Forename/Initials Surname

Post
Qualifications
Work Address

Post Code
Work Email
Work Telephone
Fax

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
The study has a duration of approximately 4.5 years. Patients are also being consented for extended follow up for an additional 10 years and the data will be held in compliance with clinical trials regulations for a period of 25 years after completion of the study.

A44. For how long will you store research data generated by the study?

Years: 30
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

The data will be stored in the Robertson Centre for Biostatistics, University of Glasgow on secure data servers and with back ups stored in fire proof safes on site and off site in a commercial data vault (Iron Mountain). Access will be controlled by the Director of the Robertson Centre for Biostatistics in accordance with the Centre's SOPs.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

◉ Yes ○ No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined.
Participants will receive reasonable travel expenses for attending study visits.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ○ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ○ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
The study will be registered onto the ISRCTN database.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☑ Internal report
- ☑ Conference presentation
- ☐ Publication on website
- ☑ Other publication
- ☑ Submission to regulatory authorities
- ☑ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

We will not publish any potentially identifiable information.

A53. Will you inform participants of the results?

(•) Yes ( ) No

Please give details of how you will inform participants or justify if not doing so.
We will provide subjects with a lay summary of the results of the study via their study site.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- [x] Independent external review
- [x] Review within a company
- [x] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The protocol has been developed by a group with extensive clinical and research experience relevant to this study

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician

☐ Review by a statistician within the Chief Investigator's institution

☑ Review by a statistician within the research team or multi−centre group

☐ Review by educational supervisor

☐ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title	Forename/Initials	Surname

Department
Institution
Work Address

Post Code
Telephone
Fax
Mobile
E-mail

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Cardiovascular mortality or hospitalisation for worsening heart failure (analysis will include first and recurrent hospitalisations)

A58. What are the secondary outcome measures?*(if any)*

1. CV mortality
2. Hospitalisation for worsening heart failure (analysis will include first and recurrent hospitalisations)
3. All cause mortality
4. CV mortality or first hospitalisation for major CV event (stroke, myocardial infarction [MI], heart failure)
5. Physical domain of QoL (Minnesota living with heart failure and EQ-5D) - this will be the difference between groups at 4 months and also at 20 months
6. Overall QoL assessment (Minnesota living with heart failure and EQ-5D) - this will be the difference between groups at 4 months and also at 20 months
7. Combined all cause mortality or first all cause unplanned hospitalisation
8. Days dead or hospitalised at two years (minimum duration of follow-up)
9. Quality-adjusted days alive and out of hospital at two years
10. CV hospitalisation (first event)
11. All-cause hospitalisation (first event)

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	1300
Total international sample size (including UK):	1300
Total in European Economic Area:	1300

Further details:

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

The anticipated primary endpoint rate in the control group is 30% in the first year and 60% by three years (median follow-up). Sample size calculations based on recurrent event analyses are complex.Therefore, conservatively, we have based them on a time to first event analysis using the Wald statistic in a Cox proportional hazards model. We estimate that 570 patients per group (yielding 631 first events) will provide 80% power to detect a hazard ratio of 0.8 (20% reduction in hazard which we believe is a clinically meaningful effect). All analyses will be conducted on an intention to treat basis. We anticipate an incomplete follow up of <1% by using national record linkage. To allow for loss of information due to non-CV mortality and potential deviation from assigned therapy during the trial, we intend to recruit 650 patients per group.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Eligible and consenting participants will be randomised with equal probability to the two groups, with randomisation stratified by recruitment context (hospital inpatient/ hospitalisations for heart failure in the previous 6 months/ others recruited from out-patient clinics) and by study site using randomised permuted blocks of variable size to minimize predictability in this open study.

Randomisation will be achieved by accessing a web based randomisation system (with a telephone interactive voice response system as alternative). The investigator will provide the participant identifier and the system will check the participant's eligibility from information already entered in the electronic case record form (eCRF) and if appropriate the randomisation group will be allocated.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

All analyses will be stratified for the context within which the participant is recruited. The primary endpoint is the composite of CV death and hospitalisations for worsening heart failure analysed as a recurrent event. This is a novel endpoint for a clinical trial and methodology for analysing such outcomes is evolving. This outcome will be analysed using a joint frailty model for mortality and hospitalisations for worsening heart failure. Robustness of the approach will be validated by calculating a p-value using a re-randomisation test. Time to first event outcomes will be analysed using Cox proportional hazards models with randomised treatment as a covariate. Statistical significance will be assessed using the Wald statistic and estimated hazard ratios for the treatment effect and their 95% confidence intervals calculated. Time to event curves will be constructed using cumulative incidence functions adjusting for competing risks where appropriate. Outcomes from the Minnesota Living with Heart Failure questionnaire will be analysed at Visit 4 and Visit 20, first using t-tests and secondly in the three recruitment context subgroups (inpatient/ recent admission/ other out-patients) using Analysis of Covariance with no imputation for missing data. Analyses will be repeated using a multiple imputation procedure. Data from the EQ-5D will be analysed at each visit and by area under the curve using similar methods. Days dead or hospitalised and quality-adjusted days alive and out of hospital will be analysed using re-randomisation tests adjusting for potential length of follow-up. Serious adverse events will be tabulated by system organ class and preferred term.
A complete statistical analysis plan will be completed and signed off before database lock.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

Title Forename/Initials Surname

Post
Qualifications

Pages 23-25, irrelevant sections of 26 and 27, removed

A64-2. Please explain how the responsibilities of sponsorship will be assigned between the co-sponsors listed in A64-1

Prior to study initiation, a non-commercially funded clinical trial co-sponsorship agreement will be put in place between The roles and liabilities each organisation will take under The Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2001:1031 are laid out in this agreement signed by both organisations. shall be responsible for carrying out the obligations and responsibilities set out in the aforementioned agreement, and shall be deemed 'sponsor' for the purposes of Part 3 of the Regulations in relation to the study. shall be responsible for carrying out the responsibilities set out in the agreement , and shall be deemed 'sponsor' for the purposes of Parts 4,5, 6and 7 of the Regulations on relation to the study.

A65. Has external funding for the research been secured?

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (•) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	British Heart Foundation
Address	Greater London House
	180 Hampstead Road
	London
Post Code	NW1 7AQ
Telephone	
Fax	
Mobile	

What is the funding stream/ programme for this research project?

are providing all of the IMP, it's distribution and a contribution towards research costs of the study (£350,000). This is an investigator initiated study and does not have a designated role or responsibility in the trial design, conduct, data analysis and interpretation, manuscript writing and dissemination of results.

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

○ Yes ◉ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title Forename/Initials Surname

Organisation
Address

Post Code
Work Email
Telephone
Fax
Mobile

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/02/2016
Planned end date: 01/02/2021
Total duration:
Years: 5 Months: 0 Days: 1

A69-2. How long do you expect the study to last in all countries?

Planned start date: 01/02/2016
Planned end date: 01/02/2021
Total duration:
Years: 5 Months: 0 Days: 1

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

End of trial is database lock. After last patient last visit record linkages will have to be carried out, all study outcomes identified and adjudicated.

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 50

Does this trial involve countries outside the EU?

○ Yes ◉ No

A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	34
☑ NHS organisations in Wales	4
☑ NHS organisations in Scotland	10
☑ HSC organisations in Northern Ireland	2
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent (private or voluntary sector) organisations	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	50

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

Research and Development Department have trial monitors. A monitoring plan for this study will be developed from a risk assessment of the study and agreed with the Governance Manager.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

Unblinded trial data will be reviewed on an ongoing basis by an Independent Data Monitoring Committee (IDMC). The primary role of the IDMC will be to protect the interests of the patients. The IDMC may recommend to the Trial Steering Committee and Co-Sponsors that the study should stop prematurely because of concerns about patient safety or conclusive evidence of overwhelming benefit. The IDMC will meet approximately every six months, with formal interim analyses for evidence of efficacy when ~40% and ~70% of the target number of primary endpoints have been adjudicated. A p-value for the primary endpoint less than 0.001 will be required in favour of the iron infusion arm to make a recommendation of overwhelming evidence of efficacy. The IDMC will take into account all results and the consistency and biological plausibility of the findings in making any recommendation. The final decision on continuing or stopping the trial will lie with the Trial Steering Committee/Co-Sponsors.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

The IDMC will meet approximately every six months, with formal interim analyses for evidence of efficacy when ~40% and ~70% of the target number of primary endpoints have been adjudicated. A p-value for the primary endpoint less than 0.001 will be required in favour of the iron infusion arm to make a recommendation of overwhelming evidence of efficacy. There are no pre-specified stopping rules for assessing safety.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (NHS sponsors only)

☑ Other insurance or indemnity arrangements will apply (give details below)

provides Legal Liability and No Fault Compensation in respect of accidental injury of any Research Subject arising out of the clinical trial

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☑ Other insurance or indemnity arrangements will apply (give details below)

The provides Legal Liability and No Fault Compensation in respect of accidental injury of any Research Subject arising out of the clinical trial

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☑ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

The provides Legal Liability and No Fault Compensation in respect of accidental injury of any Research Subject arising out of the clinical trial

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

Pages 32-38 removed

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

Blood samples

2. Who will collect the samples?

Local reseearch nurse or study doctor

3. Who will the samples be removed from?

- [x] Living donors
- [ ] The deceased

4. Will informed consent be obtained from living donors for use of the samples? *Please tick as appropriate*

In this research?

(•) Yes ( ) No

In future research?

(•) Yes ( ) No ( ) Not applicable

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

( ) Yes (•) No

8. Will the samples be stored: *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*

( ) Yes (•) No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*

(•) Yes ( ) No

If Yes, say who will have access to the code and personal information about the donor.

Restricted to identified individuals at the Robertson Centre for Biostatistics. Link will be via the numerical participant ID and barcode.

In a form in which the donor could be identifiable to researchers?

( ) Yes (•) No

9. What types of test or analysis will be carried out on the samples?

Participants in selected centres will be invited to provide consent for participation in a biomarkers sub-study. Explanatory mechanistic sub-studies will be performed utilising bio-banked plasma samples taken at baseline, 4 and 20 months. Blood will be taken at each time point and centrifuged immediately at each centre. Plasma will be separated and stored at -80° ± 10° at each centre prior to transfer to the core laboratory at the University of Leicester Department of Cardiovascular Sciences for storage and assay for biomarkers of interest. This is not mandated for

participation in the study. Interest will focus initially on biomarkers known to be associated with prognosis in chronic heart failure such as those associated with left ventricular wall stress (N-terminal proBNP); endothelial function (mid regional pro-adrenomedullin); renal dysfunction (proenkephalin). Assays for these biomarkers are established in the core laboratory.

10. Will the research involve the analysis or use of human DNA in the samples?

○ Yes ◉ No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

○ Yes ◉ No

12. If so, will arrangements be made to notify the individuals concerned?

○ Yes ○ No ◉ Not applicable

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Blood will be taken at each time point and centrifuged immediately at each centre. Plasma will be separated and stored at -80° ± 10° at each centre prior to transfer to the core laboratory at the Department of Cardiovascular Sciences, NIHR Cardiovascular Biomedical Research Unit, Glenfield Hospital, University of Leicester for storage and assay for biomarkers of interest. Access will be by appropriately trained staff under the direction of Professor Iain Squire and Ms Paulene Quinn MPhil.

14. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

☐ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☑ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☐ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

List of participating sites and declarations removed

Organisation Information Document – non-commercially sponsored studies

(Template version: 1.1)

Guidance on using this document

Please use this document to create the outline Organisation Information Document/s that you will submit with your IRAS Form. In most instances the Organisation Information Document should be localised before sharing with participating NHS / HSC organisations.

Questions/items marked with an asterisk * (Questions 1, 2,4, 7, and 11-14) must be completed prior to submission of the IRAS Form.

Items marked with a caret ^ are completed by the participating NHS / HSC organisation, after the Local Information Pack is shared and where relevant.

Remaining questions may be completed on the localised Organisation Information Document either by the sponsor or authorised delegate, or by the participating NHS / HSC organisation (or collaboratively between the two), as appropriate.

To provide an answer in the document, click in a box with the grey text (click here to enter text), choose the relevant option if presented with a drop-down list or click in the box if presented with a check-box ☐.

A separate guidance document is provided and should be consulted prior to completion of this document. Please also read the question specific guidance where present.

Location (enter text below)	**Activity** (enter text below)
XXX hospital	All study activities

Study Information

1.* IRAS Project ID	XXXXXX
2.* Full Title of the Study	xxxxx
3. Contact details of person acting on behalf of sponsor for questions relating to study set up. Please enter details of the person who is the sponsor's main point of contact for all correspondence on setting up the study at this NHS / HSC organisation. This contact may be the Sponsor, a Study Manager, Clinical Research Scientist or Study Coordinator. Where a Contract Research Organisation (CRO) or Clinical Trials Unit (CTU) has been delegated to handle set up on behalf of the sponsor, the contact at the CRO or CTU should be named here.	
Name	Enter name
Telephone Number	Enter telephone number
Email Address	Enter email address
4.* Are all participating NHS / HSC organisations undertaking the same protocol activities?	
Yes	
If 'No' give details of the activities taking place at NHS / HSC organisations that you will use this outline Organisation Information Document with. Additional outline Organisation Information Documents may be required for NHS / HSC organisations undertaking different activities.	
If no, give details	

Participating NHS / HSC Organisation Information

5. Name of Participating NHS / HSC Organisation. If this Organisation Information Document is being used as an agreement the name must be entered prior to agreement.
Enter name of participating NHS / HSC Organisation
6. Location/s*:* Please provide detail below where it is planned to undertake the research only at specified locations with the participating NHS / HSC organisation (i.e. hospital(s), GP Practice(s) and/or Research Unit(s)). It is not intended that the level of detail provided here captures individual departments within the participating NHS / HSC organisation.

7*. What is the role of the person responsible for research activities at the participating NHS / HSC organisation?

- Principal Investigators are expected to be in place at participating NHS / HSC organisations where locally employed staff take responsibility for research procedures. In this scenario Principal Investigator should be selected even for single centre studies where the Chief Investigator will also be the Principal Investigator.
- Where this is not the case, local collaborators are expected to be in place where central study staff will be present at the participating organisation to undertake research procedures (the role of the Local Collaborator is to facilitate the presence of sponsor / CRO research staff).
- Where existing data is being provided for research purposes without additional research procedures and without the presence of central research team members at participating organisation, select Chief Investigator.

Principal Investigator

8. Contact details of person responsible for research activities at this participating NHS / HSC organisation as indicated in question 7 (if known). If known, please enter the details of the person you have spoken to about their role in this study at this participating NHS / HSC organisation. If unknown, please leave blank and that person can be identified and listed here during the setup of the study.

Name	Enter name
Post / Job Title	Enter post
Name of Employing Organisation	Enter name of organisation
Email Address	Enter email address
Telephone number	Enter telephone number

Timescales

9. Predicted Start and End Dates of the Study at this Participating NHS / HSC Organisation You are invited to propose a date on which you intend to start and complete research activity at this participating NHS / HSC organisation. Alternatively, this may be left blank ahead of the Local Information Pack being shared and is for agreement during study set up at the Participating NHS / HSC Organisation.	
Predicted Start Date (activities at this organisation)	01/03/2017
Predicted End Date (activities at this organisation)	01/02/2021
For many study types the following dates are not applicable (N/A) and this may be stated in answer. Where they are applicable they should be provided by the sponsor before sharing the Local Information Pack, as indicative targets for agreement, or they may be negotiated between sponsor or authorised delegate and participating NHS / HSC organisation after sharing the pack.	
Predicted Site Initiation Visit Date	01/03/2017
Predicted Start Date for participant recruitment	13/03/2017
Predicted End Date for participants recruitment (i.e. when the study moves into "follow up" activities.)	02/03/2020
Predicted End Date for all study activities (i.e. "last patient visit" completed and study is ready to be archived.)	01/03/2022

Participant Numbers

10. How many research participants are expected at this participating NHS / HSC organisation? For studies not directly involving human participants, please indicate the number of samples or data-sets to be obtained. Please state if number of participants is per month, per year, overall, etc.
6

Study set up and delivery arrangements at Participating NHS / HSC Organisations

11*. The following are needed at the participating NHS / HSC organisation to deliver the study: e.g. specific equipment, patient/participant groups, service support, nursing time, etc. Please detail any specific requirements for participating organisations to deliver this study.
Access to ECG. Research nurse time to collect data and take study blood samples. Labs capacity to process blood samples. Suitable area for walk test.

12*. The following training will be provided by the sponsor or authorised delegate for local research team members. Where only specific team members (e.g. the Principal Investigator) will receive this training, this should be detailed below.
Administering study measures
13*. The sponsor expects that local research team members will have the following skills and where they do not have those skills that they will undertake the relevant training before undertaking the relevant study activities. It would not be usual for the sponsor to expect study specific training additional to that which it will provide. This section does however allow sponsors to state, for example, that when they expect **training in Good Clinical Practice** for appropriate team members where the study is a Clinical Trial of an Investigational Medicinal Product, they will accept UK nationally recognised GCP training, training recognised on the **Transcelerate mutual recognition scheme**, etc.
All staff on delegation log must have Trancelerate accredited GCP training. Staff taking consent should have appropriate training and/or experience in consenting study participants. Staff carrying out clinical activities such as ECG and blood tests must confirm appropriate clinical training and experience.
14*. The following funding/resources/equipment, etc. is to be provided to this participating NHS / HSC organisation. The sponsor should answer this question whether this Organisation Information Document is to be used as the agreement between participating NHS organisation or not. Where the document is intended as the agreement, further detail should be provided in Appendix 2.
All study drugs will be provided to site

Appendices

Appendix 1: General Provisions

Appendix 2: Finance Provisions

Appendix 3: Material Transfer Provisions

Appendix 4: Data Processing Agreement

Appendix 5: Data Sharing Agreement

The sponsor or authorised delegate should answer the question at the top of Appendix 1 and, if it intends this Organisation Information Document to form the agreement between itself and the participating NHS / HSC organisation, the questions that appear at the top of each subsequent appendix.

Study documents 4/7: Information from Schedule of events (modified to fit)

General Activities:

Specific Activity (drop down only present when Area of Activity selected first - or use free text if the drop-down options are not suitable)	Duration (Minutes)	Undertaken by (drop down or free text)	Day -x to -y
			Screen
Site Initiation Visit	120	Local PI/Research Nurse	Part A
Completion of remote monitoring form	45	Local PI/Research Nurse	Part B
Attend monitoring visit (Research Nurse)	90	Local PI/Research Nurse	Part A
Attend monitoring visit (PI)	30	Principal Investigator	Part A
Archiving	30	Local Research Nurse	Part A

Per Participant Activities:

Number of Participants	1300

Specific Activity (drop down only present when Area of Activity selected first - or use free text if the drop-down options are not suitable)	Duration (Minutes)	Undertaken by (drop down or free text)	Day -x	R	4 we	4 mor	8 mor	12 mo	16 mo	20 mo	48 m	Colun
			Screen	Randomisation/1st infusion	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 - 13	End of study
Identify potential partipant	10	Local Research Nurse	SSC									
Approach potential participant to discuss study	10	Local PI/Research Nurse	SSC									
Take informed consent	15	Local PI/Research Nurse	SSC									
Demographics	10	Local Research Nurse	SSC									
Medical history	30	Local Research Nurse	Part A									
Concomitant medication check (at baseline)	10	Local Research Nurse	Part A									
Concomitant medication check (concomitant)	5	Local Research Nurse			Part A	Part A	Part A	Part A	Part A	Part A	Part A	Part A
Eligibility check (exclusions)	15	Principal Investigator	SSC	SSC								
Blood sample - collection processing	20	Local PI/Research Nurse	TC									
OTHER - N-BNP (where applicable)		Local Laboratory Staff	Part A									
OTHER - TSAT (where applicable)		Local Laboratory Staff	Part A		Part A	Part A	Part A	Part A	Part A	Part A	Part A	
OTHER - Ferritin (where applicable)		Local Laboratory Staff	Part A		Part A	Part A	Part A	Part A	Part A	Part A	Part A	
Biochemistry A - creatinine/eGFR		Local Laboratory Staff	TC	TC	TC	TC	TC	TC	TC	TC	TC	
Biochemistry A - haemoglobin		Local Laboratory Staff	TC	TC	TC	TC	TC	TC	TC	TC	TC	
MCV, MCHC, MCH, RDW, platelets		Local Laboratory Staff	TC	TC		TC				TC		
OTHER - Sodium, potassium, urea		Local Laboratory Staff	TC	TC		TC				TC		
Biochemistry A - CRP		Local Laboratory Staff	TC	TC		TC				TC		
Biochemistry Profile - Full (bilirubin, albumin, random glucose)		Local Laboratory Staff	TC	TC		TC				TC		
Blood sample - collection processing (biobank)	15	Local PI/Research Nurse		Part A		Part A				Part A		
Use of IVR/IWR system for dispensing by Pharmacy (additional time)	60	Local Pharmacist		TC	TC	TC	TC	TC	TC	TC	TC	
Administer study drug in clinic (IV iron arm only as per protocol)	120	Local PI/Research Nurse		TC	TC	TC	TC	TC	TC	TC	TC	
Review/reporting of patient AEs/SAEs	10	Local PI/Research Nurse		SSC	SSC	SSC	SSC	SSC	SSC	SSC	SSC	SSC
OTHER - Infusion reactions (IV Iron arm only)	5	Local PI/Research Nurse		SSC	SSC	SSC	SSC	SSC	SSC	SSC	SSC	SSC
Subject Questionnaire MLWHF	10	Local Research Nurse		Part A		Part A				Part A		
Subject Questionnaire EQ5D	5	Local Research Nurse		Part A	Part A	Part A	Part A	Part A	Part A	Part A	Part A	Part A
Clinical assessment	15	Local PI/Research Nurse	Part A	Part A	Part A	Part A	Part A	Part A	Part A	Part A	Part A	Part A
OTHER - 6 minute walk test	10	Local PI/Research Nurse		Part A		Part A				Part A		
ECG with report	10	Principal Investigator	TC									
Pregnancy test	5	laboratory staff		Part A	Part A	Part A	Part A	Part A	Part A	Part A	Part A	Part A
CRF/eCRF completion including data transfer and query resolution	20	Local Research Nurse	Part B	Part B	Part B	Part B	Part B	Part B	Part B	Part B	Part B	Part B

Study documents 5/7 Patient Letter

Date:

Dear

THE STUDY

Many patients with heart failure have iron deficiency (people who have low iron levels or cannot use iron properly) and this may affect the way they feel. We want to test whether giving iron can improve health outcomes for patients with heart failure and reduce the likelihood of them being admitted to hospital. The British Heart Foundation supports this aim and has provided funds to help us to do the work with a major UK study.

We believe you may be eligible to participate in this study and we would like you to consider being part of it. Please find enclosed a copy of the study Patient Information Sheet.

What happens next?

- Please let the study team know whether you are interested in taking part by returning the enclosed slip in the stamped addressed envelope or by contacting [research contact at local site, number and email to be inserted].
- If you would like to ask any questions before responding please contact us using the details above and mention the Study when you call or email.
- If you decide to proceed, an appointment will be arranged to discuss the study with you and check that it is safe and appropriate for you to take part.
- Before taking part in the study, you will receive a full health check, including blood tests
- You will be seen at [insert location]; the research team can refund your travel expenses.
- Please note that responding to this letter does not commit you. You can choose not to take part at any stage. If you decide not to take part this will in no way affect your future treatment.
- If you decide to take part we will inform your GP.

Thank you for considering this request,

Yours sincerely,

Hospital Doctor (Consultant or Equivalent) name. Signature.

Study documents 6/7: Participant Information Sheet

THE STUDY

Patient Information Sheet

You are being invited to take part in a research study. Before you decide to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your relatives and friends if you wish. Please feel free to ask us if there is anything that you find unclear or if you would like more information.

What is the purpose of this research?

Patients with heart failure commonly have iron deficiency (people who have low iron levels or cannot use iron properly) and this is thought to contribute to the symptoms they experience, including shortness of breath and fatigue. Some previous studies have suggested that by correcting iron deficiency with iron injections patients may feel better. However, more information is needed to find out whether treating iron deficiency in patients with heart failure can reduce the need to be admitted to hospital for worsening heart failure and improve life expectancy. It is not currently routine practice to give iron injections when treating iron deficiency in heart failure patients.

This study is set up to investigate whether or not the use of iron injections when added to present standard treatments is better than the use of standard treatments alone.

Why have I been chosen?

You are known to have heart failure and recent tests show that the ability of your heart to pump blood is reduced. Many (up to 50%, or 1 in 2) patients with heart failure have iron deficiency. If you do have iron deficiency you may be suitable to take part in this study, to help us understand whether treatment with iron injections are helpful.

Do I have to take part?

It is up to you to decide whether or not to take part in this study. Taking part in medical research in the UK is entirely voluntary and you should feel under no pressure to take part if you do not think it is right for you.

A member of the study team will discuss the study with you and what it involves. You can then make an informed decision on whether or not you wish to take part.

You are free to withdraw from the study at any time without giving a reason. If you decide not to take part or change your mind at any time, this will not affect your current or future care in the NHS.

What will happen to me if I take part?

If you agree to take part in this study, you will be given this information sheet to keep and once the study has been explained to you (by either a doctor or a research nurse) and your questions answered, you will be asked to sign and date a Consent Form. You will be involved in the study for somewhere between two and a half and three years, depending on when you are recruited. Your personal involvement will stop after this time. You will also be asked to give permission for us to copy parts of your medical records relating to health outcomes and treatments for a further 10 years to help us to see if your involvement in the study has had long term effects on your health.

As part of an initial 'screening assessment', a doctor or research nurse will review your medical history and lifestyle factors (such as smoking and alcohol intake) including all your medications and check that it is appropriate and safe for you to be involved in the study. You will have your blood pressure, weight and height measured and we may take a blood sample to check your iron levels and heart failure condition. An ECG will be performed, unless you have had one within the last 4 weeks. Only patients with iron deficiency will proceed to any further tests or treatments in the study. This visit will take up to an hour of your time.

Sometimes we are unsure which way of treating patients is best. To find out, we need to make comparisons between different treatments. We put people into groups and give each group a different treatment. Each participant is put into a group by chance (randomly). The results are then compared between the groups.

In the study, one group of participants will receive treatment with iron injections (this is actually given through a drip into a vein over a period of 15-30 minutes). The other group of participants will not receive any iron injections as part of the study. You will have a 50:50 chance of being in the group that receives injections**. Participants in both groups will continue to receive their usual care for treatment of heart failure.**

You should only take part in the study if you are willing to accept the chance of being randomly allocated to either group. Because the groups of participants in the study are allocated by chance you cannot choose which group you would like to be in and the nurse or doctor cannot choose this either.

If you have iron deficiency and therefore are suitable to enter the study you will be invited back for a formal study visit. During this visit you will have a number of tests. You will be asked to complete two short questionnaires about your condition and how it affects your quality of life. These tests are for all participants.

The following describes what happens to the participants in the study at each study visit split depending on whether they will receive iron injections or not.

Group 1: Participants allocated to receive iron injections plus usual care

All participants who are allocated to iron injections will receive an injection at the formal study visit. The iron is given into a vein through a 'drip' in your arm over 15-30 minutes. You will then need to stay in the clinic for another 30 minutes before you can go home. This whole visit will take around 1 ½ to 2 hours.

<u>Subsequent study visits</u>
These will be arranged at convenient times at around 4 weeks and then every 4 months (that is three times a year) until the study finishes. Your blood will be tested at, or before, each study visit. At each visit there will be a clinical assessment (including checking weight, blood pressure, pulse) and the research team will ask you about symptoms, what medicines you are taking and whether you have had any medical problems since the last visit. You will be asked to fill in a quality of life questionnaire (a second questionnaire and a walking test for 6 minutes will be offered at two further time points during the study). Each visit will last around 1 hour.

You will only be given an iron injection if your iron level is found to be low. On average we expect participants will require an iron injection about once a year (this will vary between participants – some needing it more often and others less often). The iron injection (Monofer®) will normally be

given at a separate appointment although it may sometimes be possible for the iron injection to be given on the same day as your study visit. You will be expected to be in the clinic for around 1 ½ to 2 hours for each iron injection.

Group 2: Participants allocated to continue on usual care

Your blood will be tested at the formal study visit. This visit will take approximately 1 – 1 ½ hours.

Subsequent study visits
These will be arranged at convenient times at around 4 weeks and then every 4 months (that is three times a year) until the study finishes. Your blood will be tested at, or before, each study visit. At each visit there will be a clinical assessment (including
checking weight, blood pressure, pulse) and the research team will ask you about symptoms, what medicines you are taking and whether you have had any medical
problems since the last visit. You will be asked to fill in a quality of life questionnaire (a second questionnaire and a walking test for 6 minutes will be offered at two further time points during the study). Each study visit will last around 1 hour.

No other visits to your GP or hospital are needed as part of the study. If you choose to discontinue study treatment or are discontinued from study treatment, or if you have a significant change in your health, with your permission the research team may telephone, email and/or write to you for more information. You are still free to withdraw from the study at any time without giving a reason. If you decide not to take part or change your mind at any time, this will not affect your current or future care in the NHS.

We will receive information on any hospital admissions that have occurred during the study from centralised electronic NHS databases for all participants taking part in the study. We may, where available, also receive information about your health from centralised electronic systems containing details of medications you have been prescribed or, if they become available during the study, from centralised GP records. This allows us to follow up how many participants have had major problems such as heart attacks, strokes, worsening heart failure or other major illnesses. We will also receive information from centralised electronic databases on any deaths that have occurred in participants who are taking part in the study. This process is called record-linkage.

What do I have to do?

Whilst in the study there are no particular lifestyle restrictions we will ask you to follow and you will be able to continue your normal daily activities. You will continue to take your other prescribed medicines for heart failure and any other medical conditions throughout the study. The only exception to this is that we ask you not to take over the counter preparations which contain iron and if you have been allocated to receive treatment with iron injections, you should not receive prescription iron tablets while you continue to receive iron injections. If you decide to take part we will inform your GP. Please let us know at each study visit of any changes to your prescription medicines and any over-the-counter medicines you are taking regularly.

All participants will be provided with a card containing information on the study and who to contact in an emergency. You will need to carry the card with you at all times and show it to any doctor or other health care professional (e.g. nurse, pharmacist) who treats you.

If you are a woman who could become pregnant:

Oral iron supplements are safe and often taken by women during pregnancy. However, there is more limited information on use of iron injections and how this might affect an unborn baby particularly in the early stages of pregnancy. Therefore you must not take part in the study if you are breast feeding, pregnant, planning to become pregnant or are not willing to use a reliable method of contraception. If appropriate we will advise you about contraception before you decide whether to take part in the study. A pregnancy test will be performed in women of child-bearing potential before starting treatment and at each study visit where iron injections are given. If you do become pregnant during the study then you should tell the study doctor immediately. If you are in the group allocated to iron injections and stop taking these then your doctor will give you advice on how long you must continue to use contraception.

What will happen to any routine blood samples I give during the trial?

The blood samples you give during the study will be tested by a local NHS laboratory to make sure that it is safe for you to take part or continue to receive iron injections in the study. The results will be available to your clinical team. This will include haemoglobin and kidney function.

What is the drug being tested?

The iron preparation we use is called iron isomaltoside. It has been approved in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA) at a similar dose for treatment of patients who have been diagnosed with iron deficiency. It is given as an infusion into the vein over 15 – 30 minutes, depending on the dose given.

What are the alternative treatments?

At the moment there are no standard treatments for iron deficiency associated with heart failure that have been shown to have benefits on health outcomes such as the need to be admitted to hospital for worsening heart failure or improving life expectancy. If you are not chosen to receive an iron injection, the doctor looking after you might suggest iron tablets (although it is also uncertain if these have any benefit).

You may sometimes need to have further investigations to find out why you have become iron deficient.

What are the side effects of the study drug?

In general iron isomaltoside is a safe drug with few side effects and is already in regular use for treating patients with iron deficiency.

Up to 1 in 10 participants may experience a little irritation of the skin and sometimes pain at the site of the injection.

Acute, severe allergic reactions, which can be life-threatening have occurred with iron injections, but this is very rare (affects less than 1 in 10 000) and you will be carefully monitored both during and after each injection. It is uncommon, but you may experience rash, itching, nausea and shivering. If this happens the drip will be stopped immediately and you will be carefully reviewed by a doctor. Muscle and joint pains and sometimes fever may occur from hours to days after the injection. These may last for a few days, but usually get better on their own. Simple painkillers may sometimes be required. If you suffer these or any other symptoms, please inform and seek further advice from your research team.

What are the possible disadvantages and risks of taking part?

You may experience side effects related to the iron therapy as outlined above, but these are rare. Your initial screening tests may reveal that you have a medical problem of which both you and we were unaware and we may not be able to enter you into the study. Naturally, we will ensure that you receive an explanation, investigation and treatment of any new problem in the usual way. Blood sampling may cause minor discomfort and bruising.

What are the possible benefits of taking part?

If the iron treatment is successful and your iron deficiency improves or resolves completely, we are hoping that you will feel better and experience less breathlessness and fatigue and have fewer hospital admissions. However, there is no guarantee that you will benefit in any way. Nevertheless, results from this study may provide information which will help us to treat heart failure patients with iron deficiency more successfully in the future.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the drug being studied. If this happens, you will be informed by your research doctor who will discuss whether you want to continue in the study. If you decide to withdraw, your research doctor will make arrangements to ensure your care will continue as usual. If you decide to continue in the study, you may be asked to sign an updated consent form.

On receiving new information, your research doctor might consider it to be in your best interests to withdraw from the study. He or she will explain the reasons and ensure that your treatment continues as usual.

What happens when the research study stops?

At the moment, there is no clear guidance on using iron injections in the treatment of iron deficiency in heart failure patients. Therefore, once you have completed the study, your doctor will discuss the best treatment options for you – this may be the same treatment as you were using before you began the study.

What if something goes wrong?

Clinical negligence will be covered by the participating sites' own insurance schemes, while the sponsor provides Legal Liability and No Fault Compensation in respect of accidental injury of any Research Subject arising out of the clinical trial. If you are harmed in any way by taking part in this research project, there are no special compensation arrangements. If, however, you are harmed due to someone's negligence, then you may have grounds for legal action, but you may have to pay for it. Regardless of this, if you would like to complain about any aspect of the way in which you have been approached or treated during the course of this study, then you should use the normal NHS complaints mechanism, which is accessible via your local hospital services [insert local hospital complaints phone number].

Will my taking part in this study be kept confidential?

Yes, your identity will be kept confidential within the study database. None of your identifiable information will be held in the same place as the data collected for the study.

Information obtained from you for the purpose of this research will be entered into a secure database held by the Sponsor. Your completed consent form for this study will be scanned and an

electronic copy will be stored on a separate secure database. Your participation in this study will be noted in your medical records and with your consent your GP will be informed that you are taking part in this study.

If you agree to take part in the study, approved members of the study team will be able to access your medical records where it is relevant to you taking part in this study. It is a requirement that relevant sections of your medical notes and research data may be looked at by responsible individuals from research regulatory authorities, the NHS or monitors appointed by the study sponsor to check that the research is properly conducted and the interests of those taking part are adequately protected.

Will my expenses be reimbursed?

Reasonable travel costs, such as bus fares or a mileage rate of 45 pence per mile travelled, plus parking when using a personal vehicle, will be paid for visits which are directly related to participation in the study (including study visits and iron treatments).

Involvement of your General Practitioner (GP)

With your consent your GP will be notified of your participation in the trial.

What will happen to the results of the research study?

After completion of the study in 2019/2020, we hope to publish the results in a medical journal. No participants will be named or identified in any way in such a report or in any other public report and it will not be possible to identify any particular individual from these results. You will be given an option to receive the final study results or a summary of these results.

Who is organising and funding the research?

The Study has been designed by the study trial steering committee and is coordinated by the XXX Clinical Trials Unit. The study is sponsored by YYY. The Chief Investigator is ZZZ.

The study is funded by the British Heart Foundation.

A company that manufactures iron injections is providing the treatments free of charge for this study and is subsidising some of the costs of the study.

No member of the research team is being directly paid for including you in the study.

Who has reviewed the study?

The East Midlands – Leicester South Research Ethics Committee which has responsibility for scrutinising proposals for medical research on humans in the UK, has examined the proposal and has raised no objections from the point of view of medical ethics.

Please keep this information sheet for your own records. Thank you for taking the time to read this information sheet and for considering taking part in this study.

CONTACT DETAILS:

If you are interested in taking part in the study, or would like to ask any questions about the study and what it involves, please contact the local study doctor or one of our research nurses, who would be happy to answer any questions [insert contact details of local study doctor/nurse]. (These details are also given on your patient card.)

If you would like to speak to someone for impartial advice about whether or not to take part in the study or about research in general, you can contact XXXXXX

Study documents 7/7: Consent form

THE STUDY

Consent Form

CHIEF INVESTIGATOR

PRINCIPAL INVESTIGATOR

[INSERT LOCAL PI DETAILS HERE]

	Please initial box
1. I confirm that I have read and understand the information sheet, version [XXX], dated [XXX] for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. If I withdraw, I understand that the data collected whilst I was on the study will be retained and used by the research team who are obliged to keep my identity confidential.	
3. I understand that if I choose to discontinue study treatment or I am discontinued from my study treatment, or if I have a significant change in my health, the research team may telephone, email and/or write to me for more information.	
4. I understand that relevant sections of my medical notes and data collected during the study will be looked at by individuals from the study team, from regulatory authorities and from the sponsor or their appointees, where it is relevant to my taking part in this research. I give permission for these individuals, who are obliged to keep my identity confidential, to have access to my primary care, secondary care and electronic health records.	
5. I agree that information held on paper or electronically by the NHS and records maintained by the Health and Social Care Information Centre may be used to contact me during the trial.	
6. I agree to my GP being informed of my participation in the study.	
7. I agree to take part in the above study.	

OPTIONAL CONSENT

1. I agree that information held electronically by the Office of National Statistics and the Health and Social Care Information Centre will be extracted in order to follow up my health status where relevant to this study for a period of up to 10 years after the end of the trial.	
2. I would like to receive a copy of the final study results	

Name of Patient (PRINT NAME)	Date	Signature
Name of person taking consent (PRINT NAME)	Date	Signature

1 copy for patient; 1 copy to be kept in medical/ GP notes, 1 (original) for researcher site file;

1 scanned (electronic) copy to study portal.