

# Imaging intravenous iron in the body

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<b>Registration date</b> 09/12/2022	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 16/07/2024	<b>Condition category</b> Haematological Disorders	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Iron deficiency (lack of iron) is normally treated with oral iron tablets, which deliver a small amount of iron gradually over a number of weeks. In recent years, an alternative treatment based on intravenous iron (i.e. through a 'drip') has become increasingly common. This can be helpful in patients who are unable to take oral iron, or when there is a need for rapid treatment of iron deficiency e.g. before major surgery. In contrast to oral iron, intravenous iron safely delivers a large amount of iron at once. While it is an efficient way of quickly correcting iron deficiency, it is not known where in the body this large quantity of iron ends up. The aims of the study are to establish the kinetics of iron uptake into the heart, liver, spleen, kidney, skeletal muscle and blood after a single intravenous iron infusion.

### Who can participate?

Patients aged 18 years and over with anaemia and/or confirmed iron deficiency who are due to receive intravenous iron infusion (Ferinject) as part of their standard clinical care

### What does the study involve?

MRI scans and blood samples are taken at baseline (before infusion), and at 3 hours, 2 weeks and 6 weeks after the infusion.

### What are the possible benefits and risks of participating?

Blood sample collection may cause some discomfort, bruising or very minor bleeding. MRI is safe and non-invasive and does not involve any ionising radiation (x-rays).

### Where is the study run from?

Oxford University's Centre for Magnetic Resonance Imaging (OCMR), which is located on the John Radcliffe Hospital site (UK)

### When is the study starting and how long is it expected to run for?

June 2021 to December 2026

### Who is funding the study?

British Heart Foundation (UK)

Who is the main contact?

Prof. Samira Lakhal-Littleton, samira.lakhal-littleton@dpag.ox.ac.uk

## Contact information

### Type(s)

Scientific

### Contact name

Dr Samira Lakhal-Littleton

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## Additional identifiers

### EudraCT/CTIS number

Nil known

### IRAS number

308355

### ClinicalTrials.gov number

Nil known

### Secondary identifying numbers

CPMS 52957, IRAS 308355

## Study information

### Scientific Title

Study of tissue iron uptake in iron-deficient patients receiving intravenous iron replacement therapy: a prospective observational study (STUDY)

### Acronym

STUDY

### Study objectives

Intravenous iron, administered as part of standard clinical care, may increase iron levels within non-erythroid organs such as the heart and kidney.

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

Approved 10/06/2022, North West - Liverpool Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)2071048118, +44 (0)20 7104 8222, +44 (0)2071048016; liverpoolcentral.rec@hra.nhs.uk), ref: 22/NW/0172

### **Study design**

Observational; Design type: Validation of investigation /therapeutic procedures

### **Primary study design**

Observational

### **Secondary study design**

Longitudinal study

### **Study setting(s)**

Hospital

### **Study type(s)**

Treatment

### **Participant information sheet**

Not available in web format, please use the contact details to request a patient information sheet

### **Health condition(s) or problem(s) studied**

Anaemia and/or confirmed iron deficiency

### **Interventions**

This is a prospective, observational, study exploring the kinetics of tissue iron uptake following intravenous iron infusion (Ferinject), received as part of standard clinical care in a group of iron-deficient patients.

### **SCREENING, RECRUITMENT AND CONSENT**

Participants will be recruited from referrals to the Iron Deficiency Management Service (IDMS), part of Oxford University Hospitals NHS Foundation Trust (OUHFT). This service receives referrals from multiple sources across Oxfordshire. Patient referrals will be screened by members of the NHS Clinical team at IDMS to identify potentially eligible participants. Patients who would require intravenous iron as part of their standard clinical care and who are deemed eligible to participate in the study will be sent an invitation letter and patient information sheet. A few days later, a member of the NHS clinical care team at IDMS will contact the patient by telephone to check they have received the information and are happy to be contacted further about the study by a member of the study team. If so, a member of the study team will telephone the patient to explain the study, answer any questions the patients might have, check their eligibility and register verbal consent in their medical notes. They will then arrange for the participant to be given their intravenous iron, as per standard clinical care, by a member of the

NHS clinical care team at the Oxford Centre for Magnetic Resonance (OCMR), which is part of the Oxford University Medical Sciences Division, and is physically located on the John Radcliffe Hospital site. A written version of the Informed Consent form will be presented to the participant when they arrive at OCMR on day 1 of the study. Participants will be grouped into four cohorts of three so that all participants in the same cohorts are scanned on the same days. All MRI scans will also be carried out at OCMR.

#### DAY 1 - BASELINE ASSESSMENTS

Baseline clinical data for each participant:

1. Confirmation against inclusion and exclusion criteria

Baseline MRI scan (for participant #1 in each cohort; up to 3 hours):

1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2\* relaxometry of the heart, liver, spleen, blood and skeletal muscle over 3 hours

Baseline MRI scan (for participants #2 and #3 in each cohort; up to 1 hour)

1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2\* relaxometry of the heart, liver, spleen, blood and skeletal muscle over 1 hour

Baseline laboratory data:

1. In addition the research team member will collect the participant's demographic information and medical history from their medical notes
2. Haemoglobin, iron, transferrin saturation and ferritin data available from medical notes

Baseline blood samples:

1. Two collected, one as part of standard clinical care, and the other for study investigations to measure serum iron indices and serum markers of tissue iron damage.

Intravenous iron infusion:

1. Administered by a member of the clinical care team as part of standard clinical care

#### DAY 1- THREE HOURS POST-I.V. IRON INFUSION

MRI scan (up to 1 hour)

1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2\* relaxometry of the heart, liver, spleen, blood and skeletal muscle

Blood samples:

1. One sample collected for study investigations to measure serum iron indices and serum markers of tissue iron damage

#### TWO WEEK FOLLOW-UP VISIT (14 days +/-2 days)

MRI scan (up to 1 hour)

1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2\* relaxometry of the heart, liver, spleen, blood and skeletal muscle

Blood samples:

1. One sample collected for study investigations to measure serum iron indices and serum markers of tissue iron damage

## SIX WEEK FOLLOW-UP VISIT (42 days+/-2 days)

MRI scan (up to 1 hour)

1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2\* relaxometry of the heart, liver, spleen, blood and skeletal muscle

Blood samples:

1. One sample collected for study investigations to measure serum iron indices and serum markers of tissue iron damage

## DESCRIPTION OF STUDY PROCEDURES

Magnetic resonance imaging (MRI) will be performed on clinical standard MRI scanners in OCMR (at a conventional field strength of 1.5 Tesla for this study). Participants will be grouped into four cohorts of three, so that all participants in the same cohorts are scanned on the same days. Each scan will consist of MRI scanning techniques to assess cardiac structure and function by Cine MRI and organ tissue characterisation using R1/R2/R2\* relaxometry. The average duration of each MRI scan is envisaged to be around an hour. One participant in each cohort will be chosen to have an extended MRI scan at their first visit, lasting up to 3 hours. This extended MRI scan is needed to optimize the parameters for running of subsequent scans that day. All subsequent scans will be a standard duration of about an hour. This will be communicated to the participants clearly in the patient information sheet and again on day 1 when they attend OCMR for their first scan.

Research sample taking: A total of five venous blood samples will be collected from each participant, one as part of their standard clinical care, and four for study investigations. Each time, a qualified nurse will collect around 5 ml (1 teaspoon) of blood. Serum from the study will be extracted from blood samples at OCMR, then stored in a secure research -80C freezer in OCMR for all participants. At the end of the study, study serum samples will be transported to the Lakhal-Littleton Lab at the Department of Physiology, Anatomy and Genetics (DPAG), Part of the Medical Sciences Division of the University of Oxford for further investigational assays.

Investigational assays: Serum samples derived from all participants and all timepoints will be tested together. Tests include measurements of serum iron indices (iron, ferritin, transferrin and transferrin saturation) using an automated analytical Chemistry instrument (Pentra C400) in the Lakhal-Littleton Lab. Markers of tissue iron damage (including but not limited to HNE and MDA) will also be measured in serum samples using standard commercially available kits (Abcam ab118970 and ab238538 respectively).

## STATISTICAL METHODS

The primary outcome is the absolute change from baseline in MR relaxivities R1, R2, R2\* at each timepoint post Ferinject infusion, according to the following formulae:

$$\Delta R1 = R1 \text{ (at timepoint x)} - R1 \text{ (at baseline)}$$

$$\Delta R2 = R2 \text{ (at timepoint x)} - R2 \text{ (at baseline)}$$

$$\Delta R2^* = R2^* \text{ (at timepoint x)} - R2^* \text{ (at baseline)}$$

R1, R2, and R2\* values are calculated as the inverse of T1, T2, T2\* relaxation times obtained by the MR relaxometry or mapping techniques. The results will be reported as time series of average values and standard deviations (median and IQR for nonparametric variables) at each timepoint post Ferinject infusion. The presence of a statistically significant signal will be assessed using ANOVA.

The secondary outcome measure is the change from baseline in serum concentrations of iron indices (including but not limited to iron, transferrin saturation, ferritin and non-transferrin bound iron) and markers of tissue iron toxicity (including but not limited to MDA and 4-HNE). Results will be expressed both as absolute change from baseline and as percentage change relative to baseline.

Further exploratory analyses will be performed for possible interactions between the observed measures using correlations, crosscorrelations and pharmacodynamic modelling.

#### **SAMPLE SIZE CALCULATIONS**

The sample size of 12 participants was not arrived at statistically, due to a lack of information on the magnitude of effects of Ferinject on R1/R2/R2\* values at early timepoints. However, an exploratory study of MRI imaging following intravenous infusion with ultrasmall superparamagnetic particles of iron oxide (USPIO) at later timepoints used sample sizes of 5-12 participants per group. Of note, the longitudinal design involving repeated measures will increase the statistical power of the study.

#### **Intervention Type**

Other

#### **Primary outcome measure**

Cardiac structure and function (Cine MRI) and multi-organ magnetic resonance relaxometries (delta R1/R2/R2\*) measured by magnetic resonance imaging (MRI) at baseline prior to infusion (day 1), 3 h post-infusion (day 1), ~2 weeks post-infusion, and ~6 weeks post-infusion

#### **Secondary outcome measures**

1. Serum iron indices (iron, ferritin, transferrin saturation, non-transferrin bound iron) measured by standard clinical chemistry at baseline prior to infusion (day 1), 3 h post-infusion (day 1), ~2 weeks post-infusion, and ~6 weeks post-infusion
2. Serum markers of tissue iron damage, including but not limited to lipid peroxidation markers malondialdehyde (MDA) and 4- Hydroxynonenal (HNE) measured by ELISA at baseline prior to infusion (day 1), 3 h post-infusion (day 1), ~2 weeks post-infusion, and ~6 weeks post-infusion

#### **Overall study start date**

01/06/2021

#### **Completion date**

31/12/2026

## **Eligibility**

#### **Key inclusion criteria**

1. Participant is willing and able to give informed consent for participation in the study
2. Aged 18 years or above
3. Anaemia (haemoglobin less than 120 g/l for women and less than 130g/L for men) and/or confirmed iron deficiency (ferritin less than 100 mcg/l and/or transferrin saturation less than 20%)
4. Scheduled to receive intravenous iron for correction of iron deficiency

#### **Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

Planned Sample Size: 12; UK Sample Size: 12

**Total final enrolment**

13

**Key exclusion criteria**

1. Any MRI incompatible implants (e.g. cardiac, neuro, ocular implants, surgical clips, aneurysm clips, shrapnel/bullets)
2. Pregnant or lactating participants
3. Acute decompensated heart failure
4. Unstable clinical status
5. Any other medical conditions which would influence the reliability of the study results determined by the investigators
6. Any other contraindication to MRI to be confirmed by the qualified MRI operator, e.g. tattoos containing traces of metal

**Date of first enrolment**

01/10/2022

**Date of final enrolment**

31/12/2025

**Locations****Countries of recruitment**

England

United Kingdom

**Study participating centre****University of Oxford**

Oxford Centre for Clinical Magnetic Resonance Research (OCMR)

Oxford

United Kingdom

OX3 9DU

**Study participating centre**  
**John Radcliffe Hospital**  
Headley Way  
Headington  
Oxford  
United Kingdom  
OX3 9DU

## **Sponsor information**

### **Organisation**

University of Oxford

### **Sponsor details**

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Boundary Brook House  
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Headington  
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rgea.sponsor@admin.ox.ac.uk

### **Sponsor type**

University/education

### **Website**

<http://www.ox.ac.uk/>

### **ROR**

<https://ror.org/052gg0110>

## **Funder(s)**

### **Funder type**

Charity

### **Funder Name**

British Heart Foundation; Grant Codes: RE/18/3/34214

### **Alternative Name(s)**

the\_bhf, The British Heart Foundation, BHF



**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Trusts, charities, foundations (both public and private)

**Location**

United Kingdom

## Results and Publications

**Publication and dissemination plan**

Study results will be published in peer-reviewed scientific and medical journals and presented at research conferences, as soon as they are available and have been adequately analysed

**Intention to publish date**

31/12/2027

**Individual participant data (IPD) sharing plan**

The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

**IPD sharing plan summary**

Published as a supplement to the results publication

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No