THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet* 2022; published online Nov 5. https://doi.org/10.1016/S0140-6736(22)02083-9.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kalra PR, Cleland JGF, Petrie MC, et al. A randomised trial of intravenous ferric derisomaltose in patients with heart failure and iron deficiency (IRONMAN).

A randomised trial of intravenous ferric derisomaltose in patients with heart failure and iron deficiency (IRONMAN)

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FIGURES

Figure S1: Study visit attendance as a % of potential visits, by type (in-person, remote or with infusion of ferric derisomaltose) by study visit (baseline (B), week 4 (W4) and months 4 to 56 (M4-M56)), in the ferric derisomaltose arm of the study.

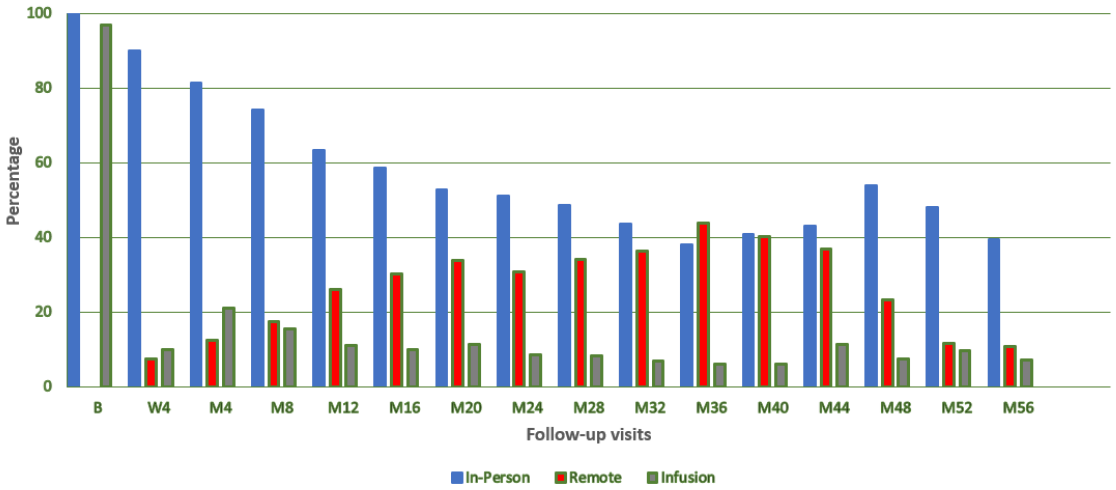


Figure S2: Study visit attendance as a % of potential visits, by type (in-person or remote) by study visit (baseline (B), week 4 (W4) and months 4 to 56 (M4-M56)), in the usual care arm of the study.

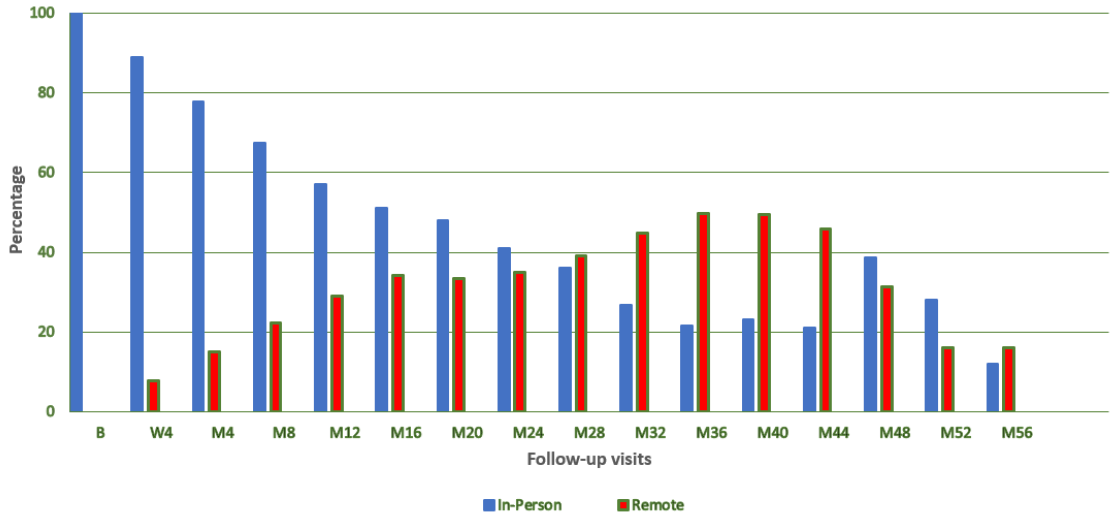


Figure S3: Mean (95% confidence interval) transferrin saturation (TSAT) by study visit (baseline (B), week4 (W4) and months 4 to 48 (M4-M48)) in the ferric derisomaltose arm.

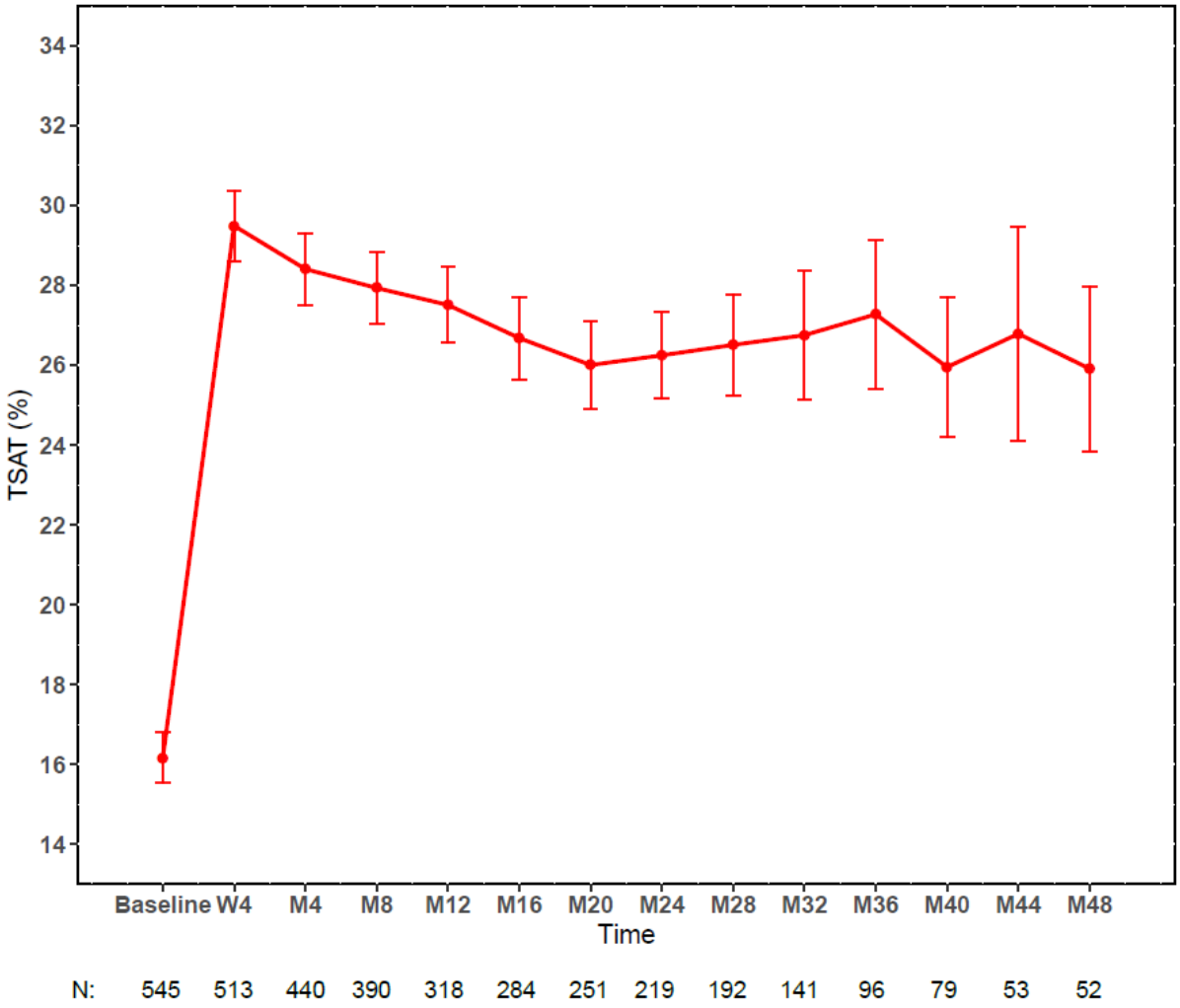
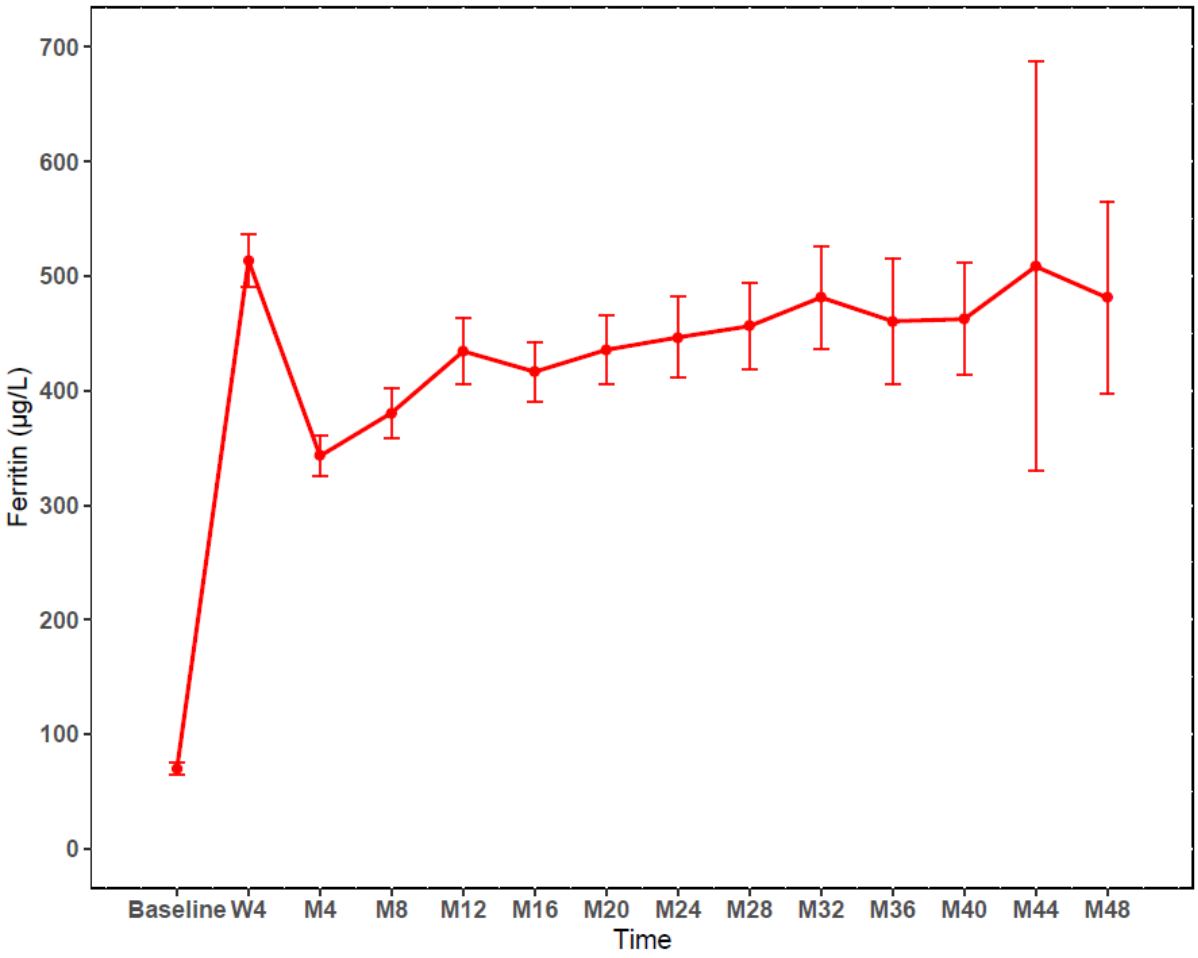
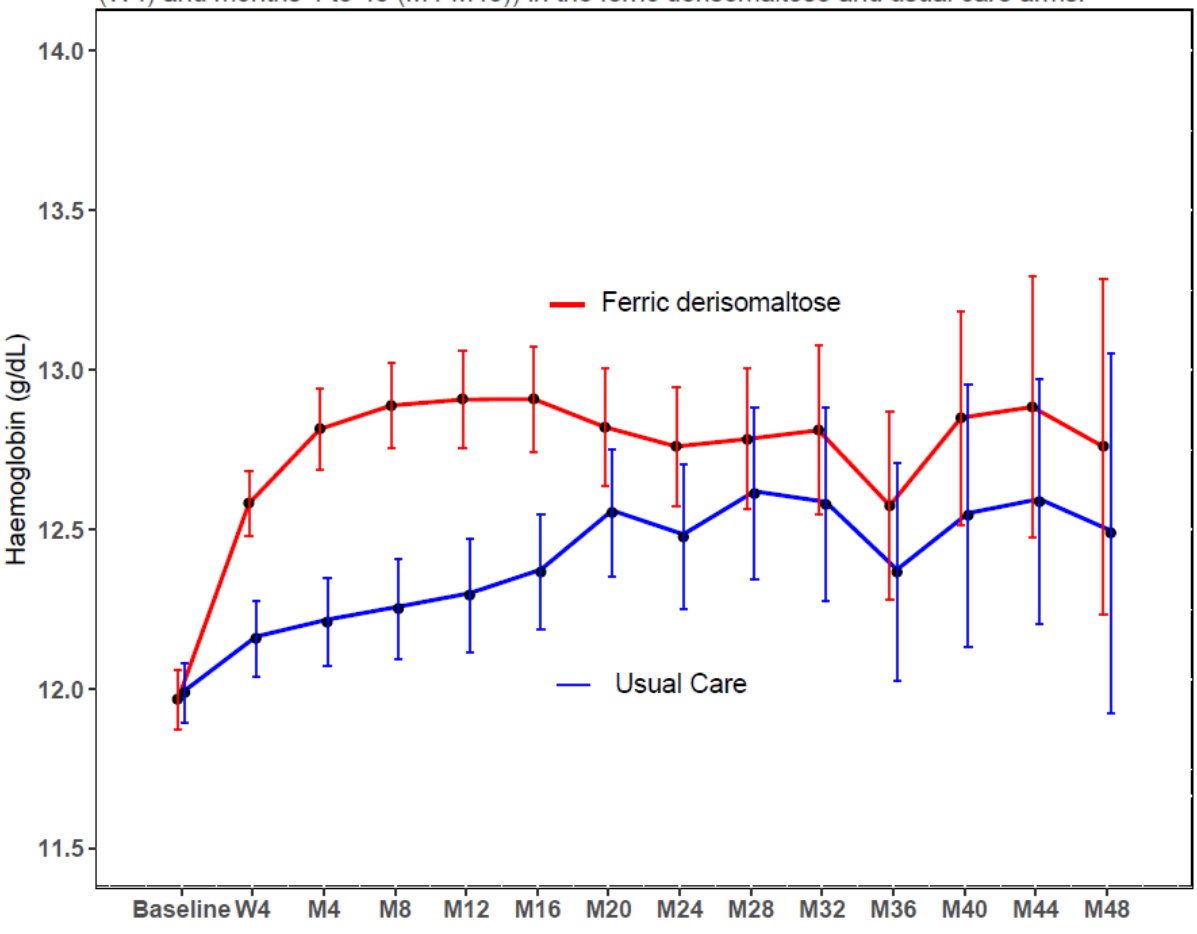


Figure S4: Mean (95% confidence interval) ferritin by study visit (baseline (B), week4 (W4) and months 4 to 48 (M4-M48)) in the ferric derisomaltose arm.



N:	559	522	443	394	325	290	258	222	197	146	103	82	57	53

Figure S5: Mean (95% confidence interval) haemoglobin by study visit (baseline (B), week4 (W4) and months 4 to 48 (M4-M48)) in the ferric derisomaltose and usual care arms.



N(Ferric derisomaltose)	559	524	448	393	332	290	261	230	205	151	108	89	57	52
N(usual care)	568	500	429	355	300	262	232	188	137	92	73	59	43	39

Figure S6: Subgroup analyses

Figure S6a

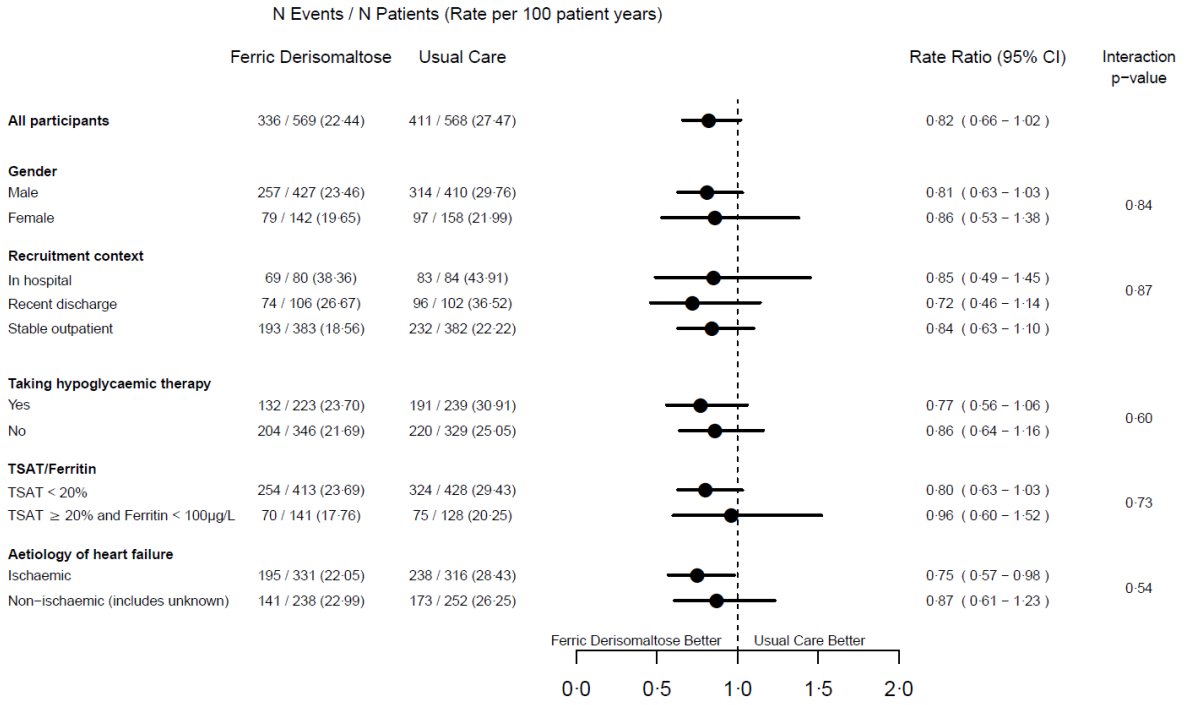
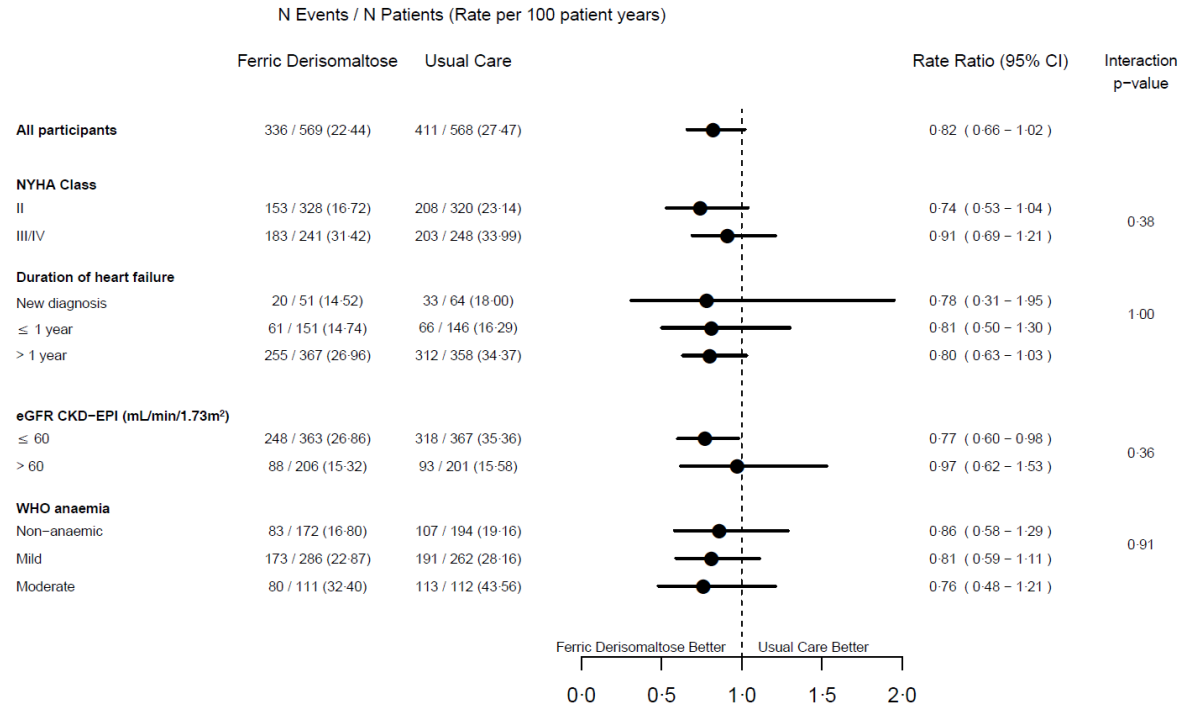


Figure S6b



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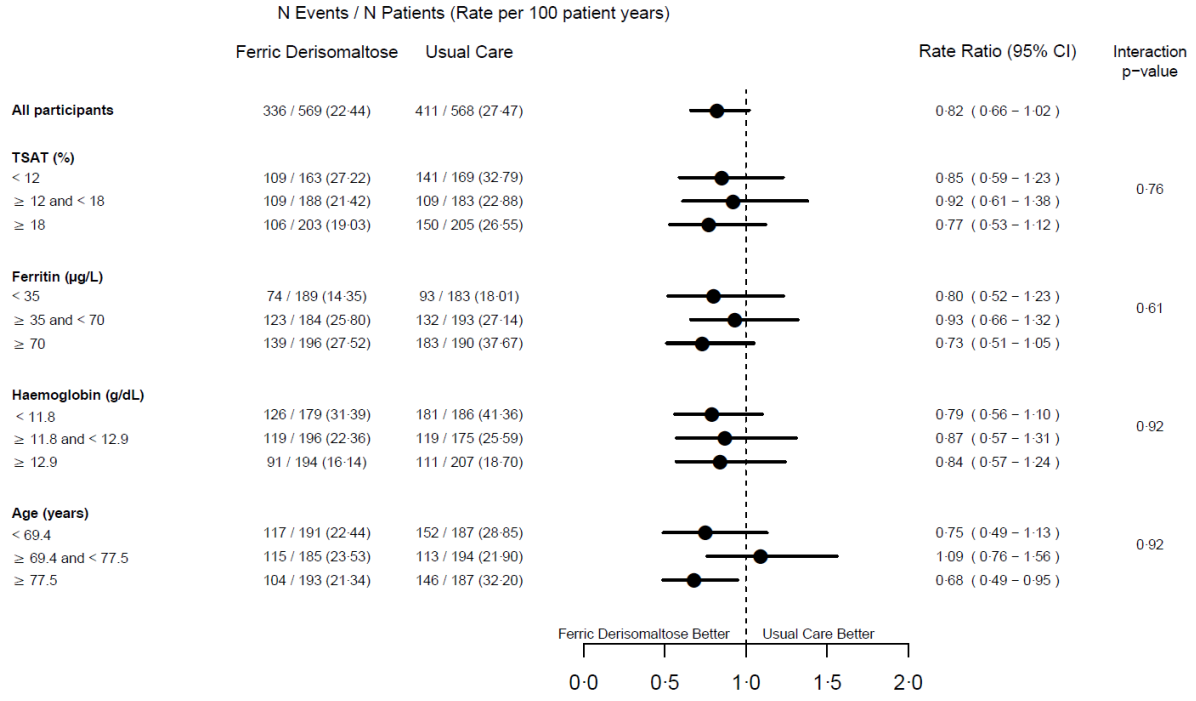
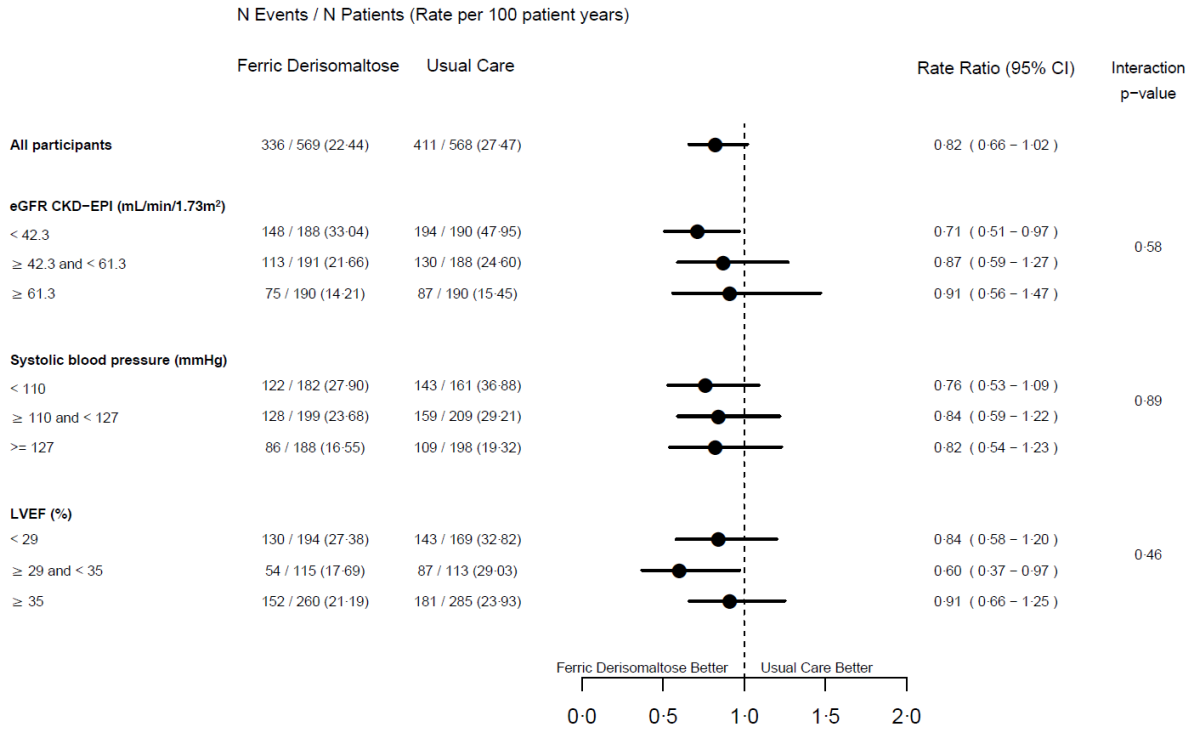


Figure S6d



TABLES

Table S1: P-values for the test of proportionality of hazards for the clinical outcomes.

Outcome	P-value
CV death and heart failure hospitalisation (recurrent event)	0·11
Heart failure hospitalisation (recurrent event)	0·11
CV death or heart failure hospitalisation (first event)	0·39
CV hospitalisation (first event)	0·46
CV death	0·80
CV death or heart failure, stroke or MI hospitalisation (first event)	0·57
All-cause death	0·66
All-cause hospitalisation (first event)	0·50
All-cause death or unplanned hospitalisation (first event)	0·77
Hospitalisation for infection (first event)	0·73
Death due to infection	0·20

Table S2: Primary and secondary endpoints in the COVID-19 analysis (censoring follow-up on March 31 2020, all comparisons are ferric derisomaltose arm relative to usual care arm.

End Point	Ferric derisomaltose (N= 527)	Usual care (N= 536)	Estimated Treatment Effect (95% CI)	P-value
Primary endpoint				
Cardiovascular death and hospitalisation for heart failure — no. of events (rate per 100 patient-yr)	167 (22·8)	230 (31·0)	0·73 (0·55 to 0·98)*	0·035
Secondary endpoints				
Hospitalisations for heart failure — no· of events (rate per 100 patient-yr)	129 (17·6)	176 (23·7)	0·74 (0·53 to 1·03)*	0·070
Cardiovascular hospitalisation — no. (%)	154 (29·2)	174 (32·5)	0·88 (0·71 to 1·10) †	0·27
Cardiovascular death or hospitalisation for heart failure — no. (%)	107 (20·3)	135 (25·2)	0·80 (0·62 to 1·03) †	0·080
Cardiovascular death — no. (%)	52 (9·9)	73 (13·6)	0·72 (0·50 to 1·02) †	0·068
Cardiovascular death or hospitalisation for stroke, myocardial infarction, or heart failure – no. (%)	119 (22·6)	146 (27·2)	0·82 (0·64 to 1·04) †	0·10
All-cause mortality — no. (%)	82 (15·6)	93 (17·4)	0·89 (0·66 to 1·20) †	0·45
All-cause hospitalisation — no. (%)	228 (43·3)	252 (47·0)	0·90 (0·76 to 1·08) †	0·27

Footnote: SE= standard error, * Rate ratio (estimated using the method of Lin, Wei, Yang, Ying [12], † Hazard ratio (estimated form Cox proportional hazards models).

Table S3: Primary and secondary endpoints in the COVID-19 analysis (censoring follow-up after one year, all comparisons are ferric derisomaltose arm relative to usual care arm.

End Point	Ferric derisomaltose (N= 527)	Usual care (N= 536)	Estimated Treatment Effect (95% CI)	P-value
Primary endpoint				
Cardiovascular death and hospitalisation for heart failure — no. of events (rate per 100 patient-yr)	97 (22·6)	149 (34·2)	0·66 (0·48 to 0·91)*	0·011
Secondary endpoints				
Hospitalisations for heart failure — no· of events (rate per 100 patient-yr)	75 (17·5)	115 (26·4)	0·66 (0·46 to 0·94)*	0·020
Cardiovascular hospitalisation — no. (%)	110 (20·9)	133 (24·8)	0·82 (0·64 to 1·06) †	0·13
Cardiovascular death or hospitalisation for heart failure — no. (%)	75 (14·2)	97 (18·1)	0·77 (0·57 to 1·05) †	0·095
Cardiovascular death — no. (%)	29 (5·5)	44 (8·2)	0·67 (0·42 to 1·07) †	0·091
Cardiovascular death or hospitalisation for stroke, myocardial infarction, or heart failure – no. (%)	82 (15·6)	105 (19·6)	0·78 (0·59 to 1·05) †	0·097
All-cause mortality — no. (%)	39 (7·4)	55 (10·3)	0·72 (0·48 to 1·08) †	0·12
All-cause hospitalisation — no. (%)	166 (31·5)	191 (35·6)	0·86 (0·70 to 1·06) †	0·17

Footnote: SE= standard error, * Rate ratio (estimated using the method of Lin, Wei, Yang, Ying [12], † Hazard ratio (estimated form Cox proportional hazards models).

Table S4: Other events of interest

Event	**Ferric derisomaltose**	**Usual Care**	**Effect 95% CI**	**P-value**
Non-SAE blood transfusions, n (rate/100 years)	62 (4·1)	93 (6·2)	0.64 (0·33, 1·24)*	0·18
Non-SAE haemorrhages, n (rate/100 years)	40 (2·7)	46 (3·1)	0.87 (0·54, 1·41)*	0·57
Deaths due to haemorrhage, n (%)	2 (0·4%)	7 (1·2%)	0.29 (0·06, 1·39) †	0·12
Hospitalisations due to haemorrhage, n (rate/100 years)	48 (3·2)	37 (2·5)	1.28 (0·71, 2·31)*	0·40

* rate ratio (estimated using a negative binomial regression model), † hazard ratio (estimated using a Cox proportional hazards model).

Table S5: Tabulation of MedDRA preferred terms for the cardiac system organ class in the Safety Population. Numbers at the counts of patients with at least one event in each category.

	Ferric derisomaltose (N=559)	**Usual care (N=568)**
Preferred term	**n (%)**	**n (%)**
All cardiac disorders	**200 (35·8%)**	**243 (42·8%)**
Cardiac failure	115 (20·6%)	118 (20·8%)
Cardiac failure congestive	33 (5·9%)	43 (7·6%)
Ventricular tachycardia	13 (2·3%)	19 (3·3%)
Acute myocardial infarction	14 (2·5%)	18 (3·2%)
Angina pectoris	12 (2·1%)	18 (3·2%)
Cardiac failure chronic	13 (2·3%)	7 (1·2%)
Atrial fibrillation	13 (2·3%)	8 (1·4%)
Myocardial infarction	6 (1·1%)	11 (1·9%)
Cardiac arrest	6 (1·1%)	15 (2·6%)
Left ventricular dysfunction	5 (0·9%)	9 (1·6%)
Angina unstable	4 (0·7%)	6 (1·1%)
Cardiorenal syndrome	6 (1·1%)	6 (1·1%)
Ventricular fibrillation	2 (0·4%)	7 (1·2%)
Acute coronary syndrome	2 (0·4%)	5 (0·9%)
Myocardial ischaemia	2 (0·4%)	5 (0·9%)
Coronary artery disease	2 (0·4%)	4 (0·7%)
Left ventricular failure	2 (0·4%)	4 (0·7%)
Arrhythmia	3 (0·5%)	2 (0·4%)
Atrial flutter	3 (0·5%)	1 (0·2%)
Congestive cardiomyopathy	2 (0·4%)	3 (0·5%)
Ischaemic cardiomyopathy	1 (0·2%)	4 (0·7%)
Atrioventricular block complete	1 (0·2%)	3 (0·5%)
Tachycardia	1 (0·2%)	1 (0·2%)
Bradycardia	2 (0·4%)	1 (0·2%)
Cardiac failure acute	1 (0·2%)	2 (0·4%)
Acute left ventricular failure	1 (0·2%)	1 (0·2%)
Atrial tachycardia	1 (0·2%)	1 (0·2%)
Cardiac tamponade	1 (0·2%)	1 (0·2%)
Cardiac ventricular thrombosis	1 (0·2%)	1 (0·2%)

	Ferric derisomaltose (N=559)	Usual care (N=568)
Preferred term	**n (%)**	**n (%)**
Hypertensive heart disease	1 (0·2%)	1 (0·2%)
Palpitations	0 (0·0%)	2 (0·4%)
Pericardial effusion	1 (0·2%)	1 (0·2%)
Right ventricular failure	2 (0·4%)	0 (0·0%)
Tachyarrhythmia	2 (0·4%)	0 (0·0%)
Ventricular arrhythmia	0 (0·0%)	2 (0·4%)
Atrioventricular block	0 (0·0%)	1 (0·2%)
Bifascicular block	0 (0·0%)	1 (0·2%)
Bundle branch block left	0 (0·0%)	1 (0·2%)
Cardiac disorder	1 (0·2%)	0 (0·0%)
Cardiomyopathy	0 (0·0%)	1 (0·2%)
Cardiovascular disorder	0 (0·0%)	1 (0·2%)
Coronary artery stenosis	0 (0·0%)	1 (0·2%)
Dressler's syndrome	0 (0·0%)	1 (0·2%)
Mitral valve incompetence	1 (0·2%)	0 (0·0%)
Myocarditis	0 (0·0%)	1 (0·2%)
Pulmonary oedema	0 (0·0%)	1 (0·2%)
Sinus arrest	0 (0·0%)	1 (0·2%)
Sinus node dysfunction	1 (0·2%)	0 (0·0%)
Supraventricular tachycardia	0 (0·0%)	1 (0·2%)
Tricuspid valve incompetence	0 (0·0%)	1 (0·2%)
Ventricular dysfunction	0 (0·0%)	1 (0·2%)
Ventricular tachyarrhythmia	0 (0·0%)	1 (0·2%)

OTHER SUPPLEMENTARY MATERIAL

Original Protocol

FULL/LONG TITLE OF THE TRIAL

Effectiveness of *I*nt*r*avenous ir*on* treat*m*ent vs standard care in p*a*tie*n*ts with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRONMAN)

SHORT STUDY TITLE / ACRONYM

*I*nt*r*avenous ir*on* treat*m*ent in p*a*tie*n*ts with heart failure and iron deficiency: IRONMAN

FULL/LONG TITLE OF THE TRIAL

Effectiveness of *I*nt*r*avenous ir*on* treat*m*ent vs standard care in p*a*tie*n*ts with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRONMAN)

SHORT STUDY TITLE / ACRONYM

***I*nt*r*avenous ir*on* treat*m*ent in p*a*tie*n*ts with heart failure and iron deficiency: IRONMAN**

PROTOCOL VERSION NUMBER AND DATE

Version 1.3 (11/02/2016)

RESEARCH REFERENCE NUMBERS

IRAS Number:	191168
EudraCT Number:	2015-004196-73
ISRCTN Number / Clinical trials.gov Number:	
SPONSORS Number:	GN15CA190
FUNDERS Number:	BHF Clinical Study no. CS/15/1/31175

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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.....
......./...../.....

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.....

Position:
.....

For and on behalf of the Study Co-Sponsor (NHS Greater Glasgow and Clyde):

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Position:
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Chief Investigator:

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TRIAL SUMMARY

Trial Title	Effectiveness of *I*ntravenous iron treatment vs standard care in patients with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRONMAN)	
Internal ref. no. (or short title)	*I*ntravenous iron treatment in patients with heart failure and iron deficiency: IRONMAN	
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	1300	
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)
Secondary	To compare the additional effect of an IV iron regimen to guideline-indicated therapy on all-cause mortality, other CV endpoints, quality of life (QoL) and assess its safety in patients with CHF secondary to left ventricular systolic dysfunction and iron deficiency.	*SECONDARY EFFICACY* 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 2.5 years (minimum duration of follow-up) 9. Quality-adjusted days alive and out of hospital at 2.5 years 10. CV hospitalisation (first event) 11. All-cause hospitalisation (first event) *SECONDARY SAFETY* 1. Death due to sepsis 2. Hospitalisation primarily for infection
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 Greater London House, 180 Hampstead Road, London NW1 7AW	£1,724,196
Pharmacosmos Roervangsvej 30, DK-4300 Holbaek	- Provision of investigational medicinal product, bio-bank and additional contribution to research costs.

ROLE OF STUDY SPONSOR AND FUNDER

NHS Greater Glasgow & Clyde and The University of Glasgow 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 NHS Greater Glasgow & Clyde and The University of Glasgow. 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. The University of Glasgow 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. NHS Greater Glasgow & Clyde 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, Glasgow 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>Pharmacosmos</u>

This is an investigator-initiated study. Pharmacosmos have provided support in terms of the investigational medicinal product (IMP) and additional financial support. Pharmacosmos 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 Pharmacosmos will be invited to attend TSC meetings as an observer. Support from Pharmacosmos will be acknowledged in any publications related to the study.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will:

1. agree the trial protocol and any protocol amendments
2. provide advice to the investigators on all aspects of the trial
3. include an independent chairperson, at least 2 other independent members, representative from the BHF and a patient or carer representative

Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the TSC who will advise the co-sponsors. The TSC will meet at the start of the study, and annually thereafter. The TSC will have its own charter outlining the role and responsibilities of its members. The TSC may invite other attendees from the trial team to present or participate in discussions on particular topics. These attendees will be non-voting members.

Independent data monitoring committee (IDMC)

An IDMC will be established to include a minimum of two independent medical experts (covering the domains of renal and cardiovascular disease; one of the academic clinicians will act as chair) and an independent biostatistician. The Glasgow CTU will liaise with the committee and ensure that the committee is provided with adequate information about study progress and results.

The IDMC will have a formal charter; this will outline the responsibilities of the IDMC members, Glasgow CTU and the co-sponsors. Responsibilities include:

• To protect the safety of patients recruited to the trial.

• Advising the TSC and co-sponsors if it is safe and appropriate to continue with the study.

• Examining information provided by the Glasgow CTU on study recruitment, adverse events and outcomes and providing reports for the Project Office to forward to the TSC, ethics committees, regulatory bodies, study co-sponsors, and the BHF.

The IDMC will receive unblinded reports on study safety data and on study progress and outcomes. The IDMC may recommend to the TSC 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 when approximately 40% and 70% of the target number of adjudicated study outcomes have been observed. Overwhelming evidence of benefit is defined as evidence of the additional benefit of IV iron as compared with standard care ($P<0.001$). A formal interim analysis for futility will enable the IDMC to make a recommendation to stop the study

prematurely in the event of a low conditional probability of a positive outcome for the study. The IDMC will take into account all results and the consistency and biological plausibility of the findings. These analyses will have no impact on the required sample size for the study.

Trial Management Group (TMG)

The trial will be coordinated from NHS Greater Glasgow & Clyde (NHS GG&C) by the IRONMAN Trial Management Group (TMG). The TMG will consist of the chief investigator, other co-applicants, project manager and representatives from the Glasgow CTU, NHS GG&C and The University of Glasgow. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

Operational Group

This group will be responsible for the day to day running of the trial and budget and will comprise the chief investigator, project manager and representatives from Glasgow CTU. It will meet at least 3 monthly, with more meetings initially and as required, and provide information and feedback to the TSC and TMG as to the progress of the study.

Clinical Endpoint Committee

Clinical events identified as potentially relevant to the designated secondary health outcomes will be assessed by a Clinical Endpoint Committee (CEC). The composition of the CEC will be determined by agreement with the funder and co-sponsors.

Protocol contributors

The protocol has been developed by a group with extensive clinical and research experience relevant to this study including the design and conduct of landmark clinical trials. This includes specialists in heart failure (HF) (Dr Paul Kalra, Professor John Cleland, Professor Iain Squire), elderly care (Dr Callum Chapman) and nephrology (Professor Philip Kalra, Professor Iain Macdougall) with expertise in IV iron management/research. Professor Ian Ford has research expertise in design, conduct, analysis and interpretation of clinical trials and epidemiological studies, in biostatistical methods and the use of novel electronic tools to enhance the conduct of clinical research. Professor Tara Dean has extensive research expertise in large-scale study development.

The IRONMAN trial has received input from, and is strongly supported by, the Heart Failure Clinical Study Group (British Cardiovascular Society/BHF/National Institute for Health Research) and the Cardiorenal study group of the UK Kidney Research consortium (UKKRC) and is highlighted to be of global importance. Patient ambassadors have been involved directly in the development of this project. Richard Mindham (patient representative on the NICE 2010 Chronic Heart Failure GDG) coordinated input from the West Middlesex patient cardiomyopathy support group. The draft protocol was also reviewed by an independent heart failure service (Gloucestershire – heart failure nurse specialists and patients, coordinated by Annie MacCallum, Head of Specialist Services). 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.

KEY WORDS:

Chronic heart failure

Iron deficiency

Left ventricular systolic dysfunction

PROBE design

Intravenous iron

LIST of CONTENTS

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
SSI	Site Specific Information
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

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 2 weeks) as part of standard clinical practice. Results must be available prior to any dosing visit.	*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*									
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	X	X	

	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 2 weeks) as part of standard clinical practice. Results must be available prior to any dosing visit.	*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.*						
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***	
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.

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

Effectiveness of *I*nt*r*avenous ir*on* treat*m*ent vs standard care in p*a*tie*n*ts with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRONMAN)

1 BACKGROUND

Heart failure causes or complicates >4% of all admissions in adults in the UK, with a median length of stay of 11 days [1,2]. Following hospitalisation with decompensated chronic heart failure (CHF), in-hospital mortality is around 10% and most will die within two years of index admission [2]. Heart failure, acute and chronic, imposes a major burden on patients, their family and carers and on the NHS. Early readmission rates are high and quality of life often markedly impaired. Many patients with CHF are anaemic (30-50% depending on the cohort studied), and low haemoglobin is associated with increased rates of heart failure hospitalisation and mortality [3]. Iron deficiency is also common in CHF patients whether (50-57%) or not (20-32%) they have anaemia and is associated with increased mortality, independent of the presence of anaemia [4-6]. Iron deficiency may be absolute or functional (reduced bio-availability of iron recycled from the reticulo-endothelial system manifest as low transferrin saturation, TSAT) [4,7,8]. In addition to involvement in erythropoiesis, iron plays a key role in oxygen utilisation and cellular oxidative metabolism [9]. Iron deficiency is a major determinant of impaired exercise capacity, symptom limitation and of quality of life (QoL) in CHF irrespective of haemoglobin [4,10].

Several small, short-term studies [11-13] suggest that intravenous (IV) iron improves symptoms, reduces N-terminal pro B-type natriuretic peptide (NT-proBNP) levels and increases left ventricular ejection fraction (LVEF) in patients with CHF and iron deficiency anaemia. The largest trial to date, FAIR-HF [14], enrolled 459 out-patients with stable CHF and iron deficiency, with or without anaemia. Treatment with IV iron (fortnightly) over 24 weeks improved symptoms, functional capacity and quality of life as compared to placebo in a double blind study design. Although FAIR-HF was not powered to evaluate 'hard' endpoints, fewer cardiovascular (CV) hospitalisations occurred in patients assigned to iron (incidence/100 patient-years: 10.4 vs 20.0, p=0.08). Unfortunately, the frequent dosing regimen used in FAIR-HF is inconvenient for patients and expensive to deliver. CONFIRM-HF (n=304), a multi-centre, double-blind, placebo-controlled trial, enrolled 304 stable symptomatic outpatients with CHF (LVEF≤45%) and iron deficiency [15]. Patients were randomised to treatment with IV iron or placebo for 52 weeks (treatment or placebo given if still iron deficient during a correction phase [baseline and 6 weeks] and then during a maintenance phase [weeks 12, 24, and 36]). The primary end-point was the change in 6-min-walk-test (6MWT) distance from baseline to week 24. The study concluded that treatment of symptomatic, iron-deficient patients with CHF resulted in improved functional capacity, symptoms and QoL.

Major gaps in our knowledge remain, including the impact of iron repletion on hospitalisation for heart failure, overall hospitalisation (an index of both morbidity and cost) and CV mortality as well as safety. As a consequence current guidelines do not make clear recommendations on treatment of iron deficiency in CHF [16].

IRONMAN is a randomised trial of IV iron powered to detect effects on morbidity, mortality and cost-effectiveness that will inform clinical management and international guidelines. It is

an investigator designed and initiated study supported by the British Heart Foundation and by an additional grant from Pharmacosmos (the manufacturer of iron isomaltoside which is approved for treating iron deficiency). It will utilise a PROBE (prospective, randomised open-label, blinded endpoint) design. Patients will be assigned to receive IV iron or not, in addition to guideline-indicated care. Patients assigned to IV iron will receive repeated doses sufficient to ensure iron repletion for the duration of the study. Robust blinding of the administration of IV iron is difficult and complex and would impair recruitment and markedly increase expense. Therefore an adjudication committee will blindly assess all study endpoints.

2 RATIONALE

Clinical studies to date have shown that IV iron is associated with an improvement in symptoms in patients with CHF and iron deficiency irrespective of haemoglobin. In order to change clinical practice and inform guidelines it is imperative to understand whether IV iron impacts on mortality and hospitalisation and is safe in the longer term. IRONMAN will therefore assess whether the addition of IV iron isomaltoside to guideline-indicated therapy for CHF reduces morbidity and mortality in patients with iron deficiency and is cost-effective. Iron isomaltoside is licenced for the treatment of iron deficiency.

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 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 not have to be fully optimised before randomisation i.e. iron is given in parallel to changes in other treatments as is common in routine clinical practice. The current proposal has received input from, and is strongly supported by, the Heart Failure Clinical Study Group (British Cardiovascular Society/British Heart Foundation/NIHR) and the Cardiorenal study group of the UK Kidney Research consortium (UKKRC) and is highlighted to be of global importance.

Current guidelines for the management of patients with CHF do not make clear recommendations on whether to treat patients with associated iron deficiency with any therapy. In clinical practice iron status is not routinely evaluated and even if iron deficiency is detected patients may receive no treatment, oral or IV iron. Due to the pathophysiological abnormalities driving iron deficiency (inflammatory immune activation with impaired ability to absorb and mobilise iron) in patients with CHF it is unlikely that oral iron will be of value. We believe the key result from IRONMAN is to establish whether iron replacement improves CV death and/or heart failure hospitalisation and as such have designed the study with IV iron (bypassing the issues with variable/impaired absorption). This also builds on the data from the FAIR-HF [14] and CONFIRM [15] studies, which both utilised an IV iron regimen.

Other aspects of heart failure care should be provided to all participants recruited to the study according to the current guidelines, irrespective as to whether they are recruited to the IV iron arm or not. Optimisation of heart failure management according to current guidelines will be recommended at each patient visit and recorded. This will include angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists.

2.1 Assessment and management of risk

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 [17] 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 CV events.

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 CV mortality and HF hospitalisation the investigators believe that the potential benefit of treatment outweighs any additional risk in these subject groups and therefore that 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 its finish 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. 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.

Iron isomaltoside 1000 is approved for treatment of iron deficiency (either absolute or functional, see section 8). The current study will include some patients without anaemia (limited to haemoglobin <13g/dL in females and <14g/dL in males) since previous studies

[14,15] have suggested benefit of IV iron irrespective of the presence of anaemia in iron deficient patients with CHF. Patients are monitored with ferritin/TSAT to avoid iron overload.

This trial is therefore categorised by the Co-Sponsors as:

- Type B = Somewhat higher than the risk of standard medical care

See Appendix 1

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

SECONDARY EFFICACY

1. Cardiovascular 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, 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 2.5 years (minimum duration of follow-up)
9. Quality-adjusted days alive and out of hospital at 2.5 years
10. CV hospitalisation (first event)
11. All-cause hospitalisation (first event)

SECONDARY SAFETY

1. Death due to sepsis
2. Hospitalisation primarily for infection

3.4 Exploratory endpoints/outcomes

(i) In order to understand the mechanism of any potential benefit of IV iron on the described endpoints the study will compare haemoglobin, platelets, serum creatinine and eGFR between the groups at 4 months, 20 months and at the end of the study (most recent value taken).

(ii) In order to understand the impact of IV iron on iron status and its relationship to any potential benefit; assessment of serum ferritin and TSAT will be compared at 4 and 20 months between groups. This analysis will only be performed on patients entering the biobank substudy.

(iii) Healthcare utilisation data will be recorded (health economic advice has been taken to ensure appropriate data are collected – see later). Should the study be positive an application will be made for funding to conduct a formal health economic analysis (this would not be justified if the study is neutral).

(iv) Extended follow-up by electronic record linkage

Patient consent for national electronic record linkage in each of the participating countries will be obtained permitting assessment of the impact of the period of randomised treatment on long-term mortality and hospital admission (analysed 2 years after study completion in the first instance).

(v) 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.

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

Due to the nature of the study with IV iron, which is dark brown, blinding is extremely challenging. As such, trial participants and care providers will not be blinded to the intervention. Outcome assessment (end point adjudication) will however be undertaken in blinded fashion. As this is an open study, no emergency unblinding system is required.

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

Heart failure:

- Aetiology (ischaemic, dilated cardiomyopathy, hypertension, valve disease, other – specify, unknown)
- History of atrial fibrillation or flutter
- LVEF: when – date off assessment, modality (echo, cardiac magnetic resonance imaging, left ventricular angiogram, other – specify), value (%)
- Duration of heart failure: specify - new diagnosis, < 1 year, > 1 year (and specify number of years)
- Prior heart failure hospitalisation (including previous admission for those patients who are currently hospitalised): never, >1 year, 6-12 months, < 6 months

Co-morbidity:

- Hypertension: Y/N
- Inflammatory disease: Y/N. If yes - rheumatoid arthritis, inflammatory bowel disease, other - specify
- Gastrointestinal (GI) tract pathology: Y/N. If yes - history of peptic ulcer, cancer, diverticular disease, other - specify
- Diagnosis of cancer in last 5 years: Y/N. If yes specify (exclude minor local skin, prostate – unless metastatic)
- Chronic obstructive pulmonary disease (COPD): Y/N
- Asthma: Y/N
- Diabetes: Y/N

Cardiovascular events and procedures
Dates for most recent event only: never, < 1 year, 1-5 years, > 5 years

- Acute coronary event (prior MI)
- CABG
- PCI
- Device (if yes: ICD, PPM, CRT-P, CRT-D)
- Valve Surgery (mechanical, bio-prosthetic)
- Primary valvular disease (if yes: aortic/mitral)
- Stroke

7.4.3 **Medication (snap shot of what patient is taking at that visit)**

Drugs for treatment of heart failure (drug classes and names and total daily doses),
Current use Y/N (preparation and daily dose). If no, has there been use in last 6/12: Y/N (if yes reason for discontinuation: intolerance/side effect, other – please specify, unknown)

- loop diuretics (if yes – furosemide, bumetanide, torosamide, other - specify)
- thiazide like diuretics (if yes – bendroflumethiazide, metolazone, other - specify)
- ACE inhibitors (if yes – enalapril, lisinopril, perindopril, ramipril, other - specify)
- Angiotensin receptor blocker: Y/N (if yes – candesartan, losartan, irbesartan, valsartan, other - specify)
- beta-blockers: Y/N (if yes - carvedilol, bisoprolol, nebivolol, other – specify)
- digoxin: Y/N
- Mineralocorticoid receptor antagonists: Y/N (if yes: spironolactone, eplerenone)
- Entresto (LCZ 696): Y/N

Drugs for treatment of diabetes:
Y/N, If yes: insulin, metformin, sulphonylureas, other – specify

Drugs for the treatment of COPD/asthma (Includes inhalers):
Y/N, If yes: inhaled steroids, inhaled bronchodilators, other – specify

Other prescribed drugs
Specifically ask about regular use of:

- Aspirin: Y/N
- Other anti-platelet agents: Y/N
- NSAIDs: Y/N
- Proton pump inhibitors: Y/N
- H-2 antagonists: Y/N
- Anti-coagulants: Y/N (if yes: warfarin, apixaban, rivaroxaban, dabigatran, edoxaban, other)
- Steroids
- Oral iron
- List any other prescribed drugs patient is regularly taking (free text box)

Over the Counter
Specifically ask about regular use of:

- Aspirin: Y/N
- NSAIDs: Y/N

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^{o}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

- As per baseline but patients in both arms should be asked regarding use of oral and IV iron.
- Heart Failure medications.
- Treatments for anaemia (including ESA)

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

- As per baseline but patients in both arms should be asked regarding use of oral and IV iron.
- Heart Failure medications.
- Treatments for anaemia (including ESA)

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

- As per baseline but patients in both arms should be asked regarding use of oral and IV iron.
- Heart Failure medications.
- Treatments for anaemia (including ESA)

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

Withdrawal from study drug

Participants may be withdrawn from the study treatment based on their own preference or based on the clinical judgement of their physician. Any such withdrawals from study treatment will be recorded on the study eCRF with a reason for withdrawal. All such participants will continue to be followed up for clinical events and will be encouraged to attend all study visits.

If participants commence dialysis post-randomisation or are judged to need regular erythropoietin stimulating agents they will be withdrawn from study treatment but continue with follow up as per study protocol.

Participants experiencing severe hypersensitivity to iron isomaltoside 1000 or other parenteral iron products should be withdrawn from the study treatment – see also flow chart (Appendix 2) for handling infusion reactions. The drug causing the hypersensitivity symptoms and the symptoms should be documented.

Postponement or interruptions of IV iron infusion

Postponement or interruptions of IV iron infusion may occur due to the participant's medical condition or other reasons. If there is evidence of significant ongoing infection as judged by the investigator, IV iron infusion should be delayed until the infection has passed or is controlled by antibiotics. Provided this is achieved within 4 weeks of original scheduled visit date then study visit and treatment may be rescheduled as soon as possible. If treatment is delayed for more than 4 weeks due to infection, then the dose is missed with review at next planned study visit.

Postponement of IV iron infusion to a later date should also occur if the participant has decompensated liver cirrhosis (investigator opinion) or active hepatitis (if serum transaminases > 3 x's upper limit of normal). The dose is missed with review at next planned study visit.

Likewise if IV iron infusion is postponed for another reason treatment should continue when clinically indicated. Provided this is achieved within 4 weeks of original scheduled visit date then study visit and treatment may be rescheduled as soon as possible. If treatment is delayed for more than 4 weeks, then the dose is missed with review at next planned study visit.

Withdrawal from the study

If participants 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 will also be consented 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. However, participants will have the right to withdraw consent for further participation and for further data collection. All other participants will be followed up for clinical events until study completion.

7.8 Storage and analysis of samples

Blood sampling for assay of biomarkers

7.8.1 Sample collection and processing

- Samples will be appropriately labelled in accordance with the trial procedures to comply with the 1998 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.
- Blood will be collected from patients consenting to participate in the biomarker substudy
- 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 4ºC. 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

8.1 Name and description of investigational medicinal product(s)

Iron (III) isomaltoside 1000 (Monofer®)

Iron (III) isomaltoside 1000 is an intravenous (IV) iron compound manufactured by Pharmacosmos A/S (Holbaek, Denmark). Iron isomaltoside 1000 is a complex between iron and a carbohydrate moiety. The carbohydrate isomaltoside 1000 is a purely linear chemical structure as shown by ^{13}C nuclear magnetic resonance (NMR) of repeating α-(1-6) linked glucopyranose residues. Thus, it is structurally different from the branched dextran polysaccharides present in iron dextran. Isomaltoside 1000 consists predominantly of 3-5 glucose units and is prepared from oligomers used for prevention of dextran-induced anaphylactic reaction. These oligomers have been chemically modified to further reduce the potential for anaphylactic/anaphylactoid reaction. Thus, isomaltoside 1000 is not a dextran and due to the low anaphylactic potential of isomaltoside 1000 there is no requirement for a test dose [19].

Iron isomaltoside 1000 has strongly bound iron within the iron isomaltoside formulation, which enables a controlled, slow release of bioavailable iron to the iron-binding proteins with only a low risk of free iron toxicity [19]. This allows flexible dosing, including high and rapid dosing.

Following IV administration, iron isomaltoside 1000 is rapidly taken up by the cells in the reticuloendothelial system, particularly in the liver and spleen. Due to its molecular weight it is not eliminated by the kidneys [20].

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

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

8.2 Legal status of iron (III) isomaltoside 1000

Iron isomaltoside 1000 is currently registered in more than 20 European countries (including UK) and in a number of countries outside Europe. In Europe, iron isomaltoside 1000 is approved for treatment of iron deficiency in patients (either absolute or functional) in whom oral iron administration is unsatisfactory or impossible or where there is a clinical need to deliver iron rapidly.

8.3 Drug storage and supply

Monofer® 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. Monofer® will be distributed by Pharmacosmos UK Ltd 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

Monofer® 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

Monofer® 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 Monofer® 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

There will be no dosage modifications.

8.8 Known drug reactions and interaction with other therapies

Participants with hypersensitivity to the active substance, to iron isomaltoside 1000, or any of its excipients and/or known serious hypersensitivity to other parenteral iron products are excluded from the trial.

8.9 Concomitant medication

Participants should not receive IV iron if assigned to standard care unless in the opinion of the treating physician it is clinically indicated (for example haemoglobin <9.0 g/dL and evidence of iron deficiency) but may receive oral iron at the discretion of the treating physicians. No interaction with other concomitant medication is considered likely to confound the results and conclusions. Participants in the IV iron treatment arm should not receive oral iron in combination with their IV iron.

8.10 Trial restrictions

Contraindications will follow the SmPC for Monofer®. Contraception should be used by women with childbearing potential. There is no requirement for contraception for the male participants.

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

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: 1. results in death 2. is life-threatening 3. requires inpatient hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability/incapacity 5. consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question
Reference Safety Information	The information used for assessing whether an adverse reaction is expected. This is contained in either the investigator's brochure or the summary of product characteristics

*Note: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 Operational definitions for (S)AEs

Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and this protocol.

All Serious Adverse Events (SAEs) occurring during the trial will be recorded in the eCRF.

Hospitalisation for the following reasons will not be considered to be SAEs:

- Routine treatment or monitoring of heart failure not associated with any deterioration in condition.
- Treatment which was elective or pre-planned, for a pre-existing non-cardiac condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications.

- Any admission to hospital or other institution for general care where there was no deterioration in condition.
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission. For the avoidance of doubt, all emergency day case treatments for heart failure or involving percutaneous coronary intervention or cardiac device insertion should be included.

The following SAEs, which are also efficacy outcome measures, will be recorded in the eCRF but excluded from immediate reporting, after assessment by the PI, to the sponsor:

- Cardiovascular mortality
- Cardiovascular hospitalisation (including hospitalisations for CV events or hospitalisation during which a CV event occurs). A cardiovascular admission will be taken to be any admission that does not have a clear non-cardiovascular cause.

Cardiovascular death and cardiovascular hospitalisation would be considered to be expected in the trial population and therefore will be excluded from immediate reporting to the sponsor unless also considered to be related to the trial medication.

If related to the trial medication these would not be considered to be SUSARs unless the severity of the event was considered to be unexpected.

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.

<u>Events of Special Interest</u>
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.

For each Event of Special Interest the following information will be recorded:

- Nature of the event
- event duration (start and end dates, if applicable)
- relationship to study drug (if applicable)

- outcome (if applicable)

Events of Special Interest will be monitored and followed up (if applicable until the event has resolved or a final outcome has been reached).

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. The following information will be collected:

- full details in medical terms and a case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- if related, whether the reaction would be considered expected or unexpected.

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

All adverse events must be assessed for seriousness**.** All SAEs must also be assessed for severity, causality and expectedness with reference to this protocol and the Reference Safety Information (RSI). This assessment is the responsibility of the PI or medically qualified designee.

Assessment of seriousness

An adverse event will be considered serious if it:

1. results in death
2. is life threatening
3. requires hospitalisation or prolongation of existing hospitalisation
4. results in persistent or significant disability or incapacity
5. consists of a congenital anomaly or birth defect
6. is otherwise considered medically significant by the investigator

Assessment of causality i.e. does the event have a "reasonable causal relationship" with trial medication. The following categories are used:

None: The event is not considered to be related to the study drug.

Possible: Although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible.

Probable: The temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug.

Definite: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause.

Assessment of expectedness.

If the event is considered to be related (possibly, probably or definitely) to the study medication, an assessment should be made of the expectedness of the reaction i.e. is the reaction a recognised adverse effect of the medication.

The expectedness of an adverse reaction is assessed against the Reference Safety Information (RSI) i.e. the information regarding expected reactions detailed in Section 4.8 (Undesirable effects) of the approved Summary of Product Characteristics for Monofer® 100mg/ml solution for injection/infusion.

Expected: consistent with the relevant product information documented in the RSI.

Unexpected: not consistent with the relevant product information documented in the RSI.

Assessment of severity

This should be assessed and described using the following categories:

- Mild-awareness of event but easily tolerated
- Moderate-discomfort enough to cause some interference with usual activity
- Severe-inability to carry out usual activity.

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)

Any SAE assigned by the PI or delegate and by the CI (on behalf of the sponsor), as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as SUSAR and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment both opinions will be provided on the report.

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.

<u>Principal Investigator (PI)</u>:

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

<u>Chief Investigator (CI)</u>

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement, confirm seriousness and causality and assign expectedness of SAEs.

3. Immediate review of all SUSARs.
4. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).
5. Using definitions in this protocol, confirm events of special interest or potential endpoints

Sponsor:

1. Central data collection and verification of AEs, SAEs, SARs and SUSARs according to the trial protocol
2. Reporting safety information to the CI or delegate for the ongoing assessment of the risk / benefit
3. Reporting safety information to the independent oversight committees identified for the trial (Independent Data Monitoring Committee (IDMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee:

In accordance with the Charter for the TSC, periodically reviewing recruitment and the overall progress of the trial and liaising with the IDMC and sponsor regarding safety issues.

Independent Data Monitoring Committee:

In accordance with the Charter for the IDMC, periodically reviewing unblinded safety data in individual cases and to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis, reporting concerns to the TSC and sponsor.

Clinical Endpoint Committee (CEC):

In accordance with the Charter for the CEC, review and classify all potential clinical endpoints in the study.

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

The iron(III) isomaltoside 1000 in Monofer® has a low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing.

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

A Development Safety Update Report (DSUR) will be submitted once a year, or on request, to MHRA and REC until the trial is declared ended. The report will be submitted within 60 days of the anniversary of the issue of the Clinical Trials Authorisation for the trial. The DSUR will be prepared by the sponsor (PV Office) in liaison with the CI and Pharmacosmos and submitted by the sponsor (PV Office).

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size 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 [21]. 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.

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

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

10.3 Statistical analysis

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.

10.4 Subgroup analyses

The primary outcome, its sub-components and CV death or hospitalisation for heart failure as a first event will be analysed in the following sub-groups.

Categorical variables:- Sex, recruitment in versus out of hospital, patients taking/not taking hypoglycaemic therapy, TSAT <20% versus ferritin <100ug/L with TSAT ≥20%.

Continuously distributed variables: by thirds of the distributions of baseline TSAT, haemoglobin, age, eGFR, systolic blood pressure, LVEF.

Results will be presented within each sub-group along with a test for treatment by sub-group interaction.

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

Unblinded trial data will be reviewed on an ongoing basis by the IDMC. The primary role of the IDMC will be to protect the interests of the patients. The IDMC may recommend to the TSC 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. 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 TSC/Co-Sponsors.

10.6 Subject population

All analyses will be carried out on an intention to treat basis based on the randomised treatment allocation.

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

The main analyses will be based on morbidity/mortality data for which imputation is not necessary. For quality of life outcomes, laboratory results or other continuous variables, results will be analysed with and without imputation. Multiple imputation procedures will be used for imputation.

10.8 Other statistical considerations.

A Statistical Analysis Plan (SAP) will be maintained as a version controlled document and will be signed off before database lock. The SAP will contain full details of all analyses along with assumptions and procedures for handling problematic or incomplete data (e.g. incomplete dates).

10.9 Economic evaluation

Funding will only be available for an economics evaluation if the study provides a positive result. A health economist has reviewed the protocol to ensure that all relevant data have been collected.

We will collect data on the assumption we will be carrying out a cost-utility analysis, comparing the arms of the study in terms of costs and Quality Adjusted Life Years (QALYs). The main resource use data we will have available will be (1) treatments for iron deficiency in each treatment arm of the study and (2) hospital admissions. In a sensitivity analysis we will test the effect of assuming each hospital admission also involves a follow-up out-patient clinic appointment and two GP consultations.

Hospital admissions will be described using Healthcare Resource Group codes and costed from national tariffs calculated by NHS England. Costs of treating iron deficiency will be calculated from a recognised source of medicines costs such as British National Formulary or MIMS.

QALYs will be calculated by converting EQ-5D scores into utility weights, and estimating area-under-the-curve for patients in each arm of the RCT.

We will calculate the difference in costs and QALYs between the treatment arms and calculate net cost per QALY gained. Costs and QALYs in future years will be discounted and sensitivity analyses will be carried out.

11 DATA HANDLING

11.1 Source Documentation

ICH GCP defines source data as: ‘All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial’. In this study, the location of the majority of the source data will be the hospital's medical records including subject case notes, laboratory records and ECGs. The source data transcribed into the eCRF from the medical records must be accurate and verifiable. For questionnaires completed by trial subjects, the completed questionnaires will be regarded as the source data location. In cases where data is transcribed directly into the eCRF and no other paper or electronic source exists, then the eCRF will be considered the source record. In these cases, these data should be prospectively documented in the medical records to ensure a full record of the trial is available at site.

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 NHS Greater Glasgow and Clyde (GG&C) 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 NHS GG&C Research Governance Manager.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (it is noted that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended (this is the Chief Investigator's responsibility).

The Chief Investigator will notify the REC of the end of the study

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

13.2 Peer review

The study protocol has been developed with expert and independent feedback from the Heart Failure Clinical Study Group (British Cardiovascular Society/BHF/NIHR) and the Cardiorenal study group of the UK Kidney Research consortium (UKKRC).

During application for funding from the British Heart Foundation the protocol underwent peer review by 7 independent experts (including heart failure specialists, nephrologists and statisticians). The application for funding the study was approved by the Chairs and Programme Grants Committee of the British Heart Foundation.

13.3 Public and Patient Involvement

Richard Mindham (patient representative on the NICE 2010 Chronic Heart Failure GDG) coordinated input from the West Middlesex patient cardiomyopathy support group. The draft protocol was also reviewed by an independent heart failure service (Gloucestershire – heart failure nurse specialists and patients, coordinated by Head of Specialist Services). 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 patients in the study.

There will be a patient representative on the TSC.

13.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee will apply for NHS permission from the site's Research & Development (R&D) department.

For any amendment that will potentially affect a site's NHS permission, the Chief Investigator/ Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D).

13.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator, Sponsor and GCTU immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

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

A "serious breach" is a breach which is likely to affect to a significant degree –

1. the safety or physical or mental integrity of the subjects of the trial; or
2. the scientific value of the trial

If any of the above occurs then the CI and Sponsor will be notified. The sponsor will notify the appropriate authorities in writing of any serious breach in accordance with their standard operating procedures.

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

A log of financial or other competing interests for the CI, PIs and committee members will be held centrally by the Trial Coordinator throughout the trial. The Trial Coordinator will request this information at the site initiation visit and at regular intervals during study conduct, and it will be made available to the Sponsor.

13.9 Indemnity

The Co-Sponsors (University of Glasgow and Greater Glasgow Health Board) 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

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the Sponsor and TSC and any required amendment forms will be submitted to the regulatory authority, ethics committee and Sponsor. The Sponsor will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Following a substantial amendment, favourable opinion/approval must be sought from the original reviewing REC, MHRA (where appropriate) and Research and Development (R&D) office prior to implementation. The Chief Investigator will be responsible for informing the Trial Management Group of all protocol 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

During the trial and in the period prior to publication of the main study results as described in the protocol, only the Glasgow CTU will have access to the full dataset. After that period, the trial Steering Committee will conduct further data analyses for a period of three years. After that time the Trial Steering Committee will consider requests from external parties for further analyses of the study data. Proposals that are scientifically well founded and have an academic basis and where relevant data extractions and analyses are appropriately funded will not be refused. These will be considered as collaborative exercises where the contributions related to study design, conduct, database creation and maintenance and data analysis will be recognised in authorship of any scientific publication. The approach we will take will be to minimise any possibility of breach of participant confidentiality. Normally this will be achieved by minimising data travel. However, for the purposes of individual patient meta-analysis and other reasons, data may be transferred to other sites. Such transfer will require assurances on information security systems at the sites that data are to be transferred to and will involve a legal data transfer agreement. A log of all data requests and subsequent data transfers will be held at the Glasgow CTU.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

The study database will be owned by the University of Glasgow and maintained on behalf of the Study investigators, represented by the Trial Steering Committee as it is constituted during and after the trial.

The study protocol and a description of the recruitment experience and participant baseline characteristics will be published before study completion. On completion of the trial, the database will be locked and analysed by staff of the Robertson Centre for Biostatistics, University of Glasgow. A final study report will be prepared and the results will be published in a major medical journal.

After the main study publications, study investigators will be invited to submit requests for further analyses of the study database. These will be reviewed and prioritised by a Publications Committee made up of the study grant holders and convened by the study co-CIs.
The British Heart Foundation and Pharmacosmos will have the right to see and comment on any results being submitted for publication. A maximum of 28 days will be given for review of major papers and 14 days for abstracts. Such comments will be considered by the Trial Steering Committee.

A lay summary of the main results of the trial will be prepared and provided to all participants via their study site investigators.
Investigators may request a copy of the study data for their participants. Providing some or all of a patient's data to that individual is at their discretion.

14.2 Authorship eligibility guidelines and any intended use of professional writers

The main results of the study will be compiled, written up and published by the study grant holders and others taking responsibility for the study results (e.g. the statistician conducting the final analysis) on behalf of the IRONMAN investigators. The IRONMAN investigators will be listed in an Appendix and will include all site PIs, all committee members and key members of relevant study coordinating groups (including the Sponsor and Glasgow CTU).

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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.

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)

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
IV administration of Iron-maltoside-1000	Immune: Hypersensitivity/ana-phylactic reactions	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	Rare	
	Increased risk of infection/oxidative stress	IDMC will specifically receive and review information on infection – related hospitalisations	Rare	
Others?				

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

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

A guide for managing hypersensitivity reactions which occur during administration of Intravenous (IV) iron.

Administration of IV iron can be complicated by hypersensitivity reactions (HSRs). The European Medicines Agency (EMA) made a statement in 2013 [ref 17], which aims to minimise the risks in box 1. Patients at particular risk of HSRs are listed in box 2. A potential protocol for managing HSRs if they do occur is shown below in Figure 2.

BOX 1 – EMA statement on risks of HSRs to IV iron*

- All IV preparations carry a small risk of reaction and can be life-threatening.
- The benefits of IV iron outweigh the risks when oral iron is inappropriate
- IV iron should only be administered if trained staff and resuscitation is available
- A test dose is not needed
- Patients should be monitored during and for at least 30 minutes after administration infusion.
- **ALL IV iron** is contraindicated in patients with previous serious HSR to any IV iron product
- **NEVER** give IV iron during the first trimester of pregnancy
- Take special care if giving IV iron to patients with known allergies or severe atopy

*European Medicines Agency. New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines. EMA/579491/2013. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500151308.pdf

BOX 2 – Patients at higher risk if given IV iron

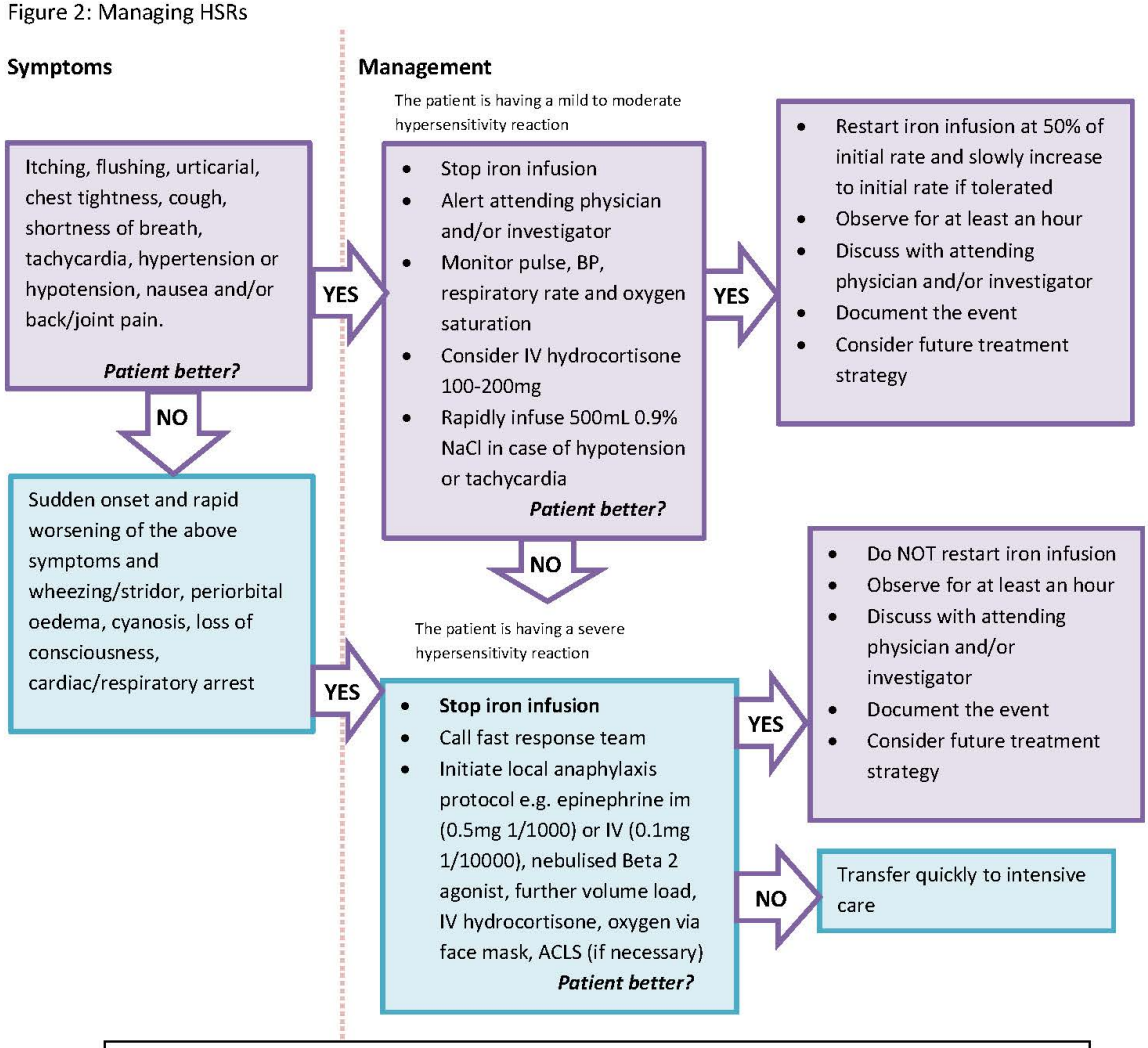
HSR more likely and/or severe

- Previous reaction to IV iron
- Fast infusion rate
- History of drug or other allergies
- Severe asthma of eczema
- Mastocytosis
- Anxiety (patient or staff)

HSR more dangerous

- Severe respiratory or cardiac disease
- Old age
- Beta-blockers, ACE inhibitors
- Pregnancy

Figure 2: Managing HSRs



Adapted from Rampton D, Folkersen J, Fishbane S et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. HAEMATOLOGICA 2014; 99 (11):1671-1676.

16.3 Appendix 3: Contraception

For women of childbearing potential in IRONMAN, acceptable forms of effective contraception include:

1. Established use of oral, injected or implanted hormonal methods of contraception
2. Placement of an intrauterine device (IUD) or intrauterine system (IUS). [Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g. steel or copper wire]
3. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) – must be combined with spermicidal foam/gel/film/cream/suppository.
4. Sole male partner has been sterilised with appropriate post-vasectomy documentation of the absence of sperm in ejaculate.
5. True abstinence: When this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, post-ovulation methods) and withdrawal are not acceptable methods of 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.

FULL/LONG TITLE OF THE TRIAL

Effectiveness of *I*nt*r*avenous ir*on* treat*m*ent vs standard care in p*a*tie*n*ts with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRONMAN)

SHORT STUDY TITLE / ACRONYM

*I*nt*r*avenous ir*on* treat*m*ent in p*a*tie*n*ts with heart failure and iron deficiency: IRONMAN

This protocol has regard for the HRA guidance and order of content

FULL/LONG TITLE OF THE TRIAL

Effectiveness of *I*nt*r*avenous ir*on* treat*m*ent vs standard care in p*a*tie*n*ts with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRONMAN)

SHORT STUDY TITLE / ACRONYM

***I*nt*r*avenous ir*on* treat*m*ent in p*a*tie*n*ts with heart failure and iron deficiency: IRONMAN**

PROTOCOL VERSION NUMBER AND DATE

Version 6.0 (15/12/2021)

RESEARCH REFERENCE NUMBERS

IRAS Number:	191168
EudraCT Number:	2015-004196-73
ISRCTN Number / Clinical trials.gov Number:	ISRCTN16403302 / NCT02642562
SPONSORS Number:	GN15CA190
FUNDERS Number:	BHF Clinical Study no. CS/15/1/31175

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Co-Sponsor (University of Glasgow):

Signature: Date:
.....
......./...../.....

Name (please print):
.....

Position:
.....

For and on behalf of the Study Co-Sponsor (NHS Greater Glasgow and Clyde):

Signature: Date:
.....
......./...../.....

Name (please print):
.....

Position:
.....

Chief Investigator:

Signature: Date:
..../...../.....

Name: (please print):
.....

Position:
.....

Statistician:

Signature: Date:
..../...../.....

Name: (please print):
.....

Position:
....

KEY TRIAL CONTACTS

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Funder(s)	**British Heart Foundation**

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Trials pharmacist	Dr Elizabeth Douglas MRPharmS Clinical Trials Pharmacist R&D Pharmacy Team Research and Development Ward 11, Dykebar Hospital Grahamston Road Paisley PA2 7DE Tel: 0141 314 4083 E-mail: elizabeth.douglas@ggc.scot.nhs.uk

TRIAL SUMMARY

Trial Title	Effectiveness of *I*ntravenous iron treatment vs standard care in patients with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRONMAN)	
Internal ref. no. (or short title)	*I*ntravenous iron treatment in patients with heart failure and iron deficiency: IRONMAN	
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	1160	
Treatment duration	Average of approximately 4 years (event driven trial, expected maximum around 5.5 years, minimum around 3 months – anticipated about 5 years recruitment and a projected further minimum of 3 months of treatment/assessments, giving a range of projected patient participation of around 3 months – 5.5 years).	
Follow up duration	Minimum of 3 months follow-up from last patient recruited, unless the study is stopped prematurely.	
Planned Trial Period	Approximately 5.5 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)
Secondary	To compare the additional effect of an IV iron regimen to guideline-indicated therapy on all-cause mortality, other CV endpoints, quality of life (QoL) and assess its safety in patients with CHF secondary to left ventricular systolic	*SECONDARY EFFICACY* 7. CV mortality 8. Hospitalisation for worsening heart failure (analysis will include first and recurrent hospitalisations) 9. All-cause mortality

	dysfunction and iron deficiency.	*10.* CV mortality or first hospitalisation for major CV event (stroke, myocardial infarction [MI], heart failure) *11.* Physical domain of QoL (Minnesota Living With Heart Failure) – this will be the difference between groups at 4 months and also at 20 months *12.* Overall QoL assessment (Minnesota Living With Heart Failure, EQ-5D index and EQ-5D VAS) – this will be the difference between groups at 4 months and also at 20 months *13.* Combined all-cause mortality or first all-cause unplanned hospitalisation *14.* Days dead or hospitalised at 3 years *15.* Quality-adjusted days alive and out of hospital at 3 years 16. CV hospitalisation (first event) 17. All-cause hospitalisation (first event) 18. 6 minute walk test - this will be the difference between groups at 4 months and also at 20 months *<u>SECONDARY SAFETY</u>* 3. Death due to infection 4. Hospitalisation primarily for infection
Investigational Medicinal Product(s)	Ferric derisomaltose	

Formulation, Dose, Route of Administration	Ferric derisomaltose (100 mg/ml) administered as an infusion up to a maximum of 20 mg / kg as follows: • Doses up to and including 1000 mg will be administered over more than 15 minutes • Doses exceeding 1000 mg must be infused over 30 minutes or more

FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
British Heart Foundation Greater London House, 180 Hampstead Road, London NW1 7AW	£1,724,196
Pharmacosmos Roervangsvej 30, DK-4300 Holbaek	- Provision of investigational medicinal product, bio-bank and additional contribution to research costs.

ROLE OF STUDY SPONSOR AND FUNDER

NHS Greater Glasgow & Clyde and The University of Glasgow 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 NHS Greater Glasgow & Clyde and The University of Glasgow. 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. The University of Glasgow 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. NHS Greater Glasgow & Clyde 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, Glasgow 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>Pharmacosmos</u>

This is an investigator-initiated study. Pharmacosmos have provided support in terms of the investigational medicinal product (IMP) and additional financial support. Pharmacosmos 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 Pharmacosmos will be invited to attend TSC meetings as an observer. Support from Pharmacosmos will be acknowledged in any publications related to the study.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will:

19. agree the trial protocol and any protocol amendments
20. provide advice to the investigators on all aspects of the trial
21. include an independent chairperson, at least 2 other independent members, representative from the BHF and a patient or carer representative

Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the TSC who will advise the co-sponsors. The TSC will meet at the start of the study, and annually (or more frequently as required) thereafter. The TSC will have its own charter outlining the role and responsibilities of its members. The TSC may invite other attendees from the trial team to present or participate in discussions on particular topics. These attendees will be non-voting members.

Independent data monitoring committee (IDMC)

An IDMC will be established to include a minimum of two independent medical experts (covering the domains of renal and cardiovascular disease; one of the academic clinicians will act as chair) and an independent biostatistician. The Glasgow CTU will liaise with the committee and ensure that the committee is provided with adequate information about study progress and results.

The IDMC will have a formal charter; this will outline the responsibilities of the IDMC members, Glasgow CTU and the co-sponsors. Responsibilities include:

• To protect the safety of patients recruited to the trial.

• Advising the TSC and co-sponsors if it is safe and appropriate to continue with the study.

• Examining information provided by the Glasgow CTU on study recruitment, adverse events and outcomes and providing reports for the Project Office to forward to the TSC, ethics committees, regulatory bodies, study co-sponsors, and the BHF.

The IDMC will receive unblinded reports on study safety data and on study progress and outcomes. The IDMC may recommend to the TSC 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 when approximately 50% and 70% of the target number of adjudicated study outcomes have been observed. Overwhelming evidence of benefit is defined as evidence of the additional benefit of IV iron as compared with standard care ($P<0.001$). A formal interim analysis for futility will enable the IDMC to make a recommendation to stop the study

prematurely in the event of a low conditional probability of a positive outcome for the study. The IDMC will take into account all results and the consistency and biological plausibility of the findings. These analyses will have no impact on the required sample size for the study.

Trial Management Group (TMG)

The trial will be coordinated from NHS Greater Glasgow & Clyde (NHS GG&C) by the IRONMAN Trial Management Group (TMG). The TMG will consist of the chief investigator, other co-applicants, project manager and representatives from the Glasgow CTU, NHS GG&C and The University of Glasgow. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

Operational Group

This group will be responsible for the day to day running of the trial and budget and will comprise the chief investigator, project manager and representatives from Glasgow CTU. It will meet at least 3 monthly, with more meetings initially and as required, and provide information and feedback to the TSC and TMG as to the progress of the study.

Clinical Endpoint Committee

Clinical events identified as potentially relevant to the designated secondary health outcomes will be assessed by a Clinical Endpoint Committee (CEC). The composition of the CEC will be determined by agreement with the funder and co-sponsors.

Protocol contributors

The protocol has been developed by a group with extensive clinical and research experience relevant to this study including the design and conduct of landmark clinical trials. This includes specialists in heart failure (HF) (Professor Paul Kalra, Professor John Cleland, Professor Iain Squire), elderly care (Dr Callum Chapman) and nephrology (Professor Philip Kalra, Professor Iain Macdougall) with expertise in IV iron management/research. Professor Ian Ford has research expertise in design, conduct, analysis and interpretation of clinical trials and epidemiological studies, in biostatistical methods and the use of novel electronic tools to enhance the conduct of clinical research.

The IRONMAN trial has received input from, and is strongly supported by, the Heart Failure Clinical Study Group (British Cardiovascular Society/BHF/National Institute for Health Research) and the Cardiorenal study group of the UK Kidney Research consortium (UKKRC) and is highlighted to be of global importance. Patient ambassadors have been involved directly in the development of this project. Richard Mindham (patient representative on the NICE 2010 Chronic Heart Failure GDG) coordinated input from the West Middlesex patient cardiomyopathy support group. The draft protocol was also reviewed by an independent heart failure service (Gloucestershire – heart failure nurse specialists and patients, coordinated by Annie MacCallum, Head of Specialist Services). 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.

KEY WORDS:

Chronic heart failure

Iron deficiency

Left ventricular systolic dysfunction

PROBE design

Intravenous iron

LIST of CONTENTS

LIST OF ABBREVIATIONS

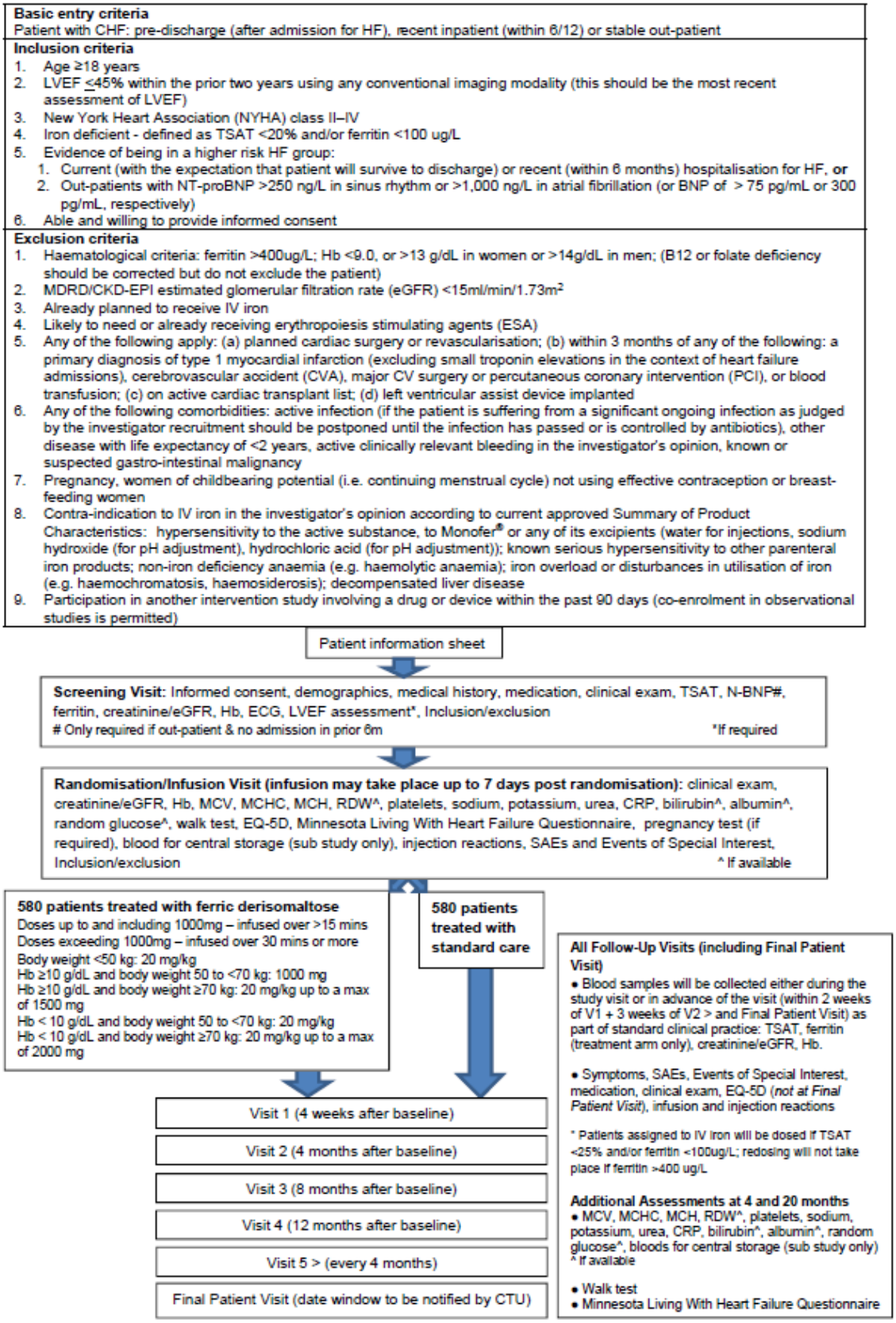
Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

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
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
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
SSI	Site Specific Information
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



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 >	Final patient visit
Time from inclusion	*For hospitalised participants, these visits will be close together prior to discharge.* *For all participants, screening and randomisation must be completed using blood tests within 6 weeks of the respective visit.* *First infusion may be administered up to 7 days post-randomisation.*		4 weeks	4 months	8 months	12 months	16 months	20 months	24 months and then 4-monthly until notified to schedule the final patient visit	*To be completed at participant's scheduled Final patient visit. Visit window to be notified by the CTU. LPLV is expected to be approximately 5.5 years from first randomisation.*
			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.	*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.* *As the study is event driven, the final patient visit cannot be pre-specified.*						
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*									
TSAT	X		X**	X**	X**	X**	X**	X**	X**	X**
Ferritin	X		X**	X**	X**	X**	X**	X**	X**	X**

	Screening	Randomisation/ First Infusion	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7 >	Final patient visit
Time from inclusion	*For hospitalised participants, these visits will be close together prior to discharge.* *For all participants, screening and randomisation must be completed using blood tests within 6 weeks of the respective visit.* *First infusion may be administered up to 7 days post-randomisation.*		4 weeks	4 months	8 months	12 months	16 months	20 months	24 months and then 4-monthly until notified to schedule the final patient visit	*To be completed at participant's scheduled Final patient visit. Visit window to be notified by the CTU. LPLV is expected to be approximately 5.5 years from first randomisation.*
			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.	*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.* *As the study is event driven, the final patient visit cannot be pre-specified.*						
Creatinine/eGFR	X	X^^	X	X	X	X	X	X	X	X
Haemoglobin	X	X^^	X	X	X	X	X	X	X	X
MCV, MCHC, MCH		X^^		X				X		
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***	X***
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**

	Screening	Randomisation/ First Infusion	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7 >	Final patient visit
Time from inclusion	*For hospitalised participants, these visits will be close together prior to discharge.* *For all participants, screening and randomisation must be completed using blood tests within 6 weeks of the respective visit.* *First infusion may be administered up to 7 days post-randomisation.*		4 weeks	4 months	8 months	12 months	16 months	20 months	24 months and then 4-monthly until notified to schedule the final patient visit	*To be completed at participant's scheduled Final patient visit. Visit window to be notified by the CTU. LPLV is expected to be approximately 5.5 years from first randomisation.*
			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.	*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.* *As the study is event driven, the final patient visit cannot be pre-specified.*						
Minnesota questionnaire		X		X				X		
EQ-5D		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[++]
LVEF assessment[#]	X									

Notes:

9. X = assessments made as part of standard clinical practice for patients with chronic heart failure
10. X* = outpatients only without admission in last 6 months
11. X** = active treatment arm (iron) only i.e. 50% of recruits
12. ^ = if available
13. ^^ = use values from assessments within 6 weeks of randomisation if available
14. + = unless there are ECG results in the last 4 weeks prior to the visit
15. [++] = for women of child-bearing potential receiving IMP.
16. *** = 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.
17. [#] = If required – an assessment can be carried out if not done in prior 2 years, or most recent result does not permit inclusion

Visits 7 to the final patient visit will be held at 4-monthly intervals.

(Note a ‘month’ is defined as a calendar month.)

STUDY PROTOCOL

Effectiveness of *I*nt*r*avenous ir*on* treat*m*ent vs standard care in p*a*tie*n*ts with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRONMAN)

1 BACKGROUND

Heart failure causes or complicates >4% of all admissions in adults in the UK, with a median length of stay of 11 days [1,2]. Following hospitalisation with decompensated chronic heart failure (CHF), in-hospital mortality is around 10% and most will die within two years of index admission [2]. Heart failure, acute and chronic, imposes a major burden on patients, their family and carers and on the NHS. Early readmission rates are high and quality of life often markedly impaired. Many patients with CHF are anaemic (30-50% depending on the cohort studied), and low haemoglobin is associated with increased rates of heart failure hospitalisation and mortality [3]. Iron deficiency is also common in CHF patients whether (50-57%) or not (20-32%) they have anaemia and is associated with increased mortality, independent of the presence of anaemia [4-6]. Iron deficiency may be absolute or functional (reduced bio-availability of iron recycled from the reticulo-endothelial system manifest as low transferrin saturation, TSAT) [4,7,8]. In addition to involvement in erythropoiesis, iron plays a key role in oxygen utilisation and cellular oxidative metabolism [9]. Iron deficiency is a major determinant of impaired exercise capacity, symptom limitation and of quality of life (QoL) in CHF irrespective of haemoglobin [4,10].

Several small, short-term studies [11-13] suggest that intravenous (IV) iron improves symptoms, reduces N-terminal pro B-type natriuretic peptide (NT-proBNP) levels and increases left ventricular ejection fraction (LVEF) in patients with CHF and iron deficiency anaemia. The largest trial to date, FAIR-HF [14], enrolled 459 out-patients with stable CHF and iron deficiency, with or without anaemia. Treatment with IV iron (fortnightly) over 24 weeks improved symptoms, functional capacity and quality of life as compared to placebo in a double blind study design. Although FAIR-HF was not powered to evaluate 'hard' endpoints, fewer cardiovascular (CV) hospitalisations occurred in patients assigned to iron (incidence/100 patient-years: 10.4 vs 20.0, p=0.08). Unfortunately, the frequent dosing regimen used in FAIR-HF is inconvenient for patients and expensive to deliver. CONFIRM-HF (n=304), a multi-centre, double-blind, placebo-controlled trial, enrolled 304 stable symptomatic outpatients with CHF (LVEF≤45%) and iron deficiency [15]. Patients were randomised to treatment with IV iron or placebo for 52 weeks (treatment or placebo given if still iron deficient during a correction phase [baseline and 6 weeks] and then during a maintenance phase [weeks 12, 24, and 36]). The primary end-point was the change in 6-min-walk-test (6MWT) distance from baseline to week 24. The study concluded that treatment of symptomatic, iron-deficient patients with CHF resulted in improved functional capacity, symptoms and QoL.

Major gaps in our knowledge remain, including the impact of iron repletion on hospitalisation for heart failure, overall hospitalisation (an index of both morbidity and cost) and CV mortality as well as safety. As a consequence current guidelines do not make clear recommendations on treatment of iron deficiency in CHF [16].

IRONMAN is a randomised trial of IV iron powered to detect effects on morbidity, mortality and cost-effectiveness that will inform clinical management and

international guidelines. It is an investigator designed and initiated study supported by the British Heart Foundation and by an additional grant from Pharmacosmos (the manufacturer of Monofer®, ferric derisomaltose, which is approved for treating iron deficiency). It will utilise a PROBE (prospective, randomised open-label, blinded endpoint) design. Patients will be assigned to receive IV iron or not, in addition to guideline-indicated care. Patients assigned to IV iron will receive repeated doses sufficient to ensure iron repletion for the duration of the study. Robust blinding of the administration of IV iron is difficult and complex and would impair recruitment and markedly increase expense. Therefore an adjudication committee will blindly assess all study endpoints.

2 RATIONALE

Clinical studies to date have shown that IV iron is associated with an improvement in symptoms in patients with CHF and iron deficiency irrespective of haemoglobin. In order to change clinical practice and inform guidelines it is imperative to understand whether IV iron impacts on mortality and hospitalisation and is safe in the longer term. IRONMAN will therefore assess whether the addition of IV ferric derisomaltose to guideline-indicated therapy for CHF reduces morbidity and mortality in patients with iron deficiency and is cost-effective. Ferric derisomaltose is licenced for the treatment of iron deficiency.

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 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 not have to be fully optimised before randomisation i.e. iron is given in parallel to changes in other treatments as is common in routine clinical practice. The current proposal has received input from, and is strongly supported by, the Heart Failure Clinical Study Group (British Cardiovascular Society/British Heart Foundation/NIHR) and the Cardiorenal study group of the UK Kidney Research consortium (UKKRC) and is highlighted to be of global importance.

Current guidelines for the management of patients with CHF do not make clear recommendations on whether to treat patients with associated iron deficiency with any therapy. In clinical practice iron status is not routinely evaluated and even if iron deficiency is detected patients may receive no treatment, oral or IV iron. Due to the pathophysiological abnormalities driving iron deficiency (inflammatory immune activation with impaired ability to absorb and mobilise iron) in patients with CHF it is unlikely that oral iron will be of value. We believe the key result from IRONMAN is to establish whether iron replacement improves CV death and/or heart failure hospitalisation and as such have designed the study with IV iron (bypassing the issues with variable/impaired absorption). This also builds on the data from the

FAIR-HF [14] and CONFIRM [15] studies, which both utilised an IV iron regimen.

Other aspects of heart failure care should be provided to all participants recruited to the study according to the current guidelines, irrespective as to whether they are recruited to the IV iron arm or not. Optimisation of heart failure management according to current guidelines will be recommended at each patient visit and recorded. This will include angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists.

2.1 Assessment and management of risk

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 ferric derisomaltose, 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 [17] 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 ferric derisomaltose 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 CV events.

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 CV mortality and HF hospitalisation the investigators believe that the potential benefit of treatment outweighs any additional risk in these subject groups and therefore that 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 its finish 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. 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.

Ferric derisomaltose is approved for treatment of iron deficiency (either absolute or functional, see section 8). The current study will include some patients without anaemia (limited to haemoglobin <13g/dL in females and <14g/dL in males) since previous studies [14,15] have suggested benefit of IV iron irrespective of the presence of anaemia in iron deficient patients with CHF. Patients are monitored with ferritin/TSAT to avoid iron overload.

This trial is therefore categorised by the Co-Sponsors as:

• Type B = Somewhat higher than the risk of standard medical care

See Appendix 1

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

Hypothesis

Addition of IV ferric derisomaltose 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

SECONDARY EFFICACY

1. Cardiovascular 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, MI, heart failure)
5. Physical domain of QoL (Minnesota Living With Heart Failure) – this will be the difference between groups at 4 months and also at 20 months
6. Overall QoL assessment (Minnesota Living With Heart Failure, EQ-5D index and EQ-5D VAS) – 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 3 years
9. Quality-adjusted days alive and out of hospital at 3 years
10. CV hospitalisation (first event)
11. All-cause hospitalisation (first event)
12. 6 minute walk test - this will be the difference between groups at 4 months and also at 20 months

SECONDARY SAFETY

1. Death due to infection
2. Hospitalisation primarily for infection

3.4 Exploratory endpoints/outcomes

(i) In order to understand the mechanism of any potential benefit of IV iron on the described endpoints the study will compare haemoglobin, platelets, serum creatinine and eGFR between the groups at 4 months and 20 months, with all but platelets also assessed at the patient's last measurement.

(ii) In order to understand the impact of IV iron on iron status and its relationship to any potential benefit; assessment of serum ferritin and TSAT will be compared at approximately 4 and 20 months between groups. This analysis will only be performed on patients entering the biobank substudy.

(iii) Healthcare utilisation data will be recorded (health economic advice has been taken to ensure appropriate data are collected – see later). Should the study be positive an application will be made for funding to conduct a formal health economic analysis (this would not be justified if the study is neutral).

(iv) Extended follow-up by electronic record linkage

Patient consent for national electronic record linkage in each of the participating countries will be obtained permitting assessment of events in the year prior to inclusion in the study and impact of the period of randomised treatment on long-term mortality and hospital admission (analysed at 1 and 2 years after the last patient follow-up).

(v) 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. (Note that if a patient's 4 or 20 month visit has taken place remotely during the COVID-19 pandemic, the biobank bloods may be taken at the next available visit (see section 7.8.1).). 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. Additional assays may be carried out at other laboratories. Material transfer agreements will be required before the transfer of samples to other laboratories.

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 ferric derisomaltose 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 in up to 100 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 prior two years using any conventional imaging modality (this should be the most recent assessment of LVEF)
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 the expectation that patient will survive to discharge) 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/CKD-EPI estimated glomerular filtration rate (eGFR) <15ml/min/1.73m^2
3. Already planned to receive IV iron
4. Likely to need or already receiving erythropoiesis stimulating agents (ESA)
5. Any of the following apply: (a) planned cardiac surgery or revascularisation; (b) within 3 months of any of the following: 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), or blood transfusion; (c) on active cardiac transplant list; (d) 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 investigator's 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 disease.
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.

The patient must have LVEF measured within the last two years (this may be done after the patient has consented to the study) and the most recent measure must be ≤45%.

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 only be performed specifically for the purposes of this study if the patient has given their consent for the study. Most patients are expected to qualify for this study on the basis of prior measurements of LVEF.

The majority of patients will have contemporary blood investigations. For screening purposes haemoglobin and eGFR assessed for clinical purposes within the last 6

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 6 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. All patients will have at least 24 hours to review the patient information sheet before being approached for consent. 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 and retrospective linkage for one year prior to consent. 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 Re-screening post-consent

Patients may fail screening post-consent, due to one or more blood results falling outside the study parameters. In these circumstances, re-testing of bloods will be permitted once for each patient.

If the initial consent was signed within 2 months of the re-testing, new consent is not required unless the consent form template has been updated in this period. If the initial consent was not signed within 2 months of re-testing then consent should be sought again.

Patients should keep the same 5-digit Patient ID and the data should be amended on the web portal as appropriate. Note that, if applicable, the new consent form will need to be scanned and uploaded to the secure study database.

7.1.5 Randomisation

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

Due to the nature of the study with IV iron, which is dark brown, blinding is extremely challenging. As such, trial participants and care providers will not be blinded to the intervention. Outcome assessment (end point adjudication) will however be undertaken in blinded fashion. As this is an open study, no emergency unblinding system is required.

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

Heart failure:

- Aetiology (ischaemic, dilated cardiomyopathy, hypertension, valve disease, congenital, other – specify, unknown)
- History of atrial fibrillation or flutter
- LVEF: when – date of assessment, modality (echo, cardiac magnetic resonance imaging, left ventricular angiogram, other – specify), value (%)
- Duration of heart failure: specify - new diagnosis, <= 1 year, >1 year (and specify number of years)
- Prior heart failure hospitalisation (including previous admission for those patients who are currently hospitalised): never, >1 year, 6-12 months, < 6 months

Co-morbidity:

- Hypertension: Y/N
- Inflammatory disease: Y/N. If yes - rheumatoid arthritis, inflammatory bowel disease, other - specify
- Gastrointestinal (GI) tract pathology: Y/N. If yes - history of peptic ulcer, cancer, diverticular disease, other - specify
- Diagnosis of cancer in last 5 years: Y/N. If yes specify (exclude minor local skin, prostate – unless metastatic)

- Chronic obstructive pulmonary disease (COPD): Y/N
- Asthma: Y/N
- Diabetes: Y/N

Cardiovascular events and procedures
Dates for most recent event only: never, < 1 year, 1-5 years, > 5 years

- Acute coronary event (prior MI)
- CABG
- PCI
- Device (if yes: ICD, PPM, CRT-P, CRT-D)
- Valve Surgery (mechanical, bio-prosthetic)
- Primary valvular disease (if yes: aortic/mitral)
- Stroke

7.4.3 Medication (snap shot of what patient is taking at that visit)

Drugs for treatment of heart failure (drug classes and names and total daily doses), Current use Y/N (preparation and daily dose). If no, has there been use in last 6/12: Y/N (if yes reason for discontinuation: intolerance/side effect, other – please specify, unknown)

- loop diuretics (if yes – furosemide, bumetanide, torosamide, other - specify)
- thiazide like diuretics (if yes – bendroflumethiazide, metolazone, other - specify)
- ACE inhibitors (if yes – enalapril, lisinopril, perindopril, ramipril, other - specify)
- Angiotensin receptor blocker: Y/N (if yes – candesartan, losartan, irbesartan, valsartan, other - specify)
- beta-blockers: Y/N (if yes - carvedilol, bisoprolol, nebivolol, other – specify)
- digoxin: Y/N
- Mineralocorticoid receptor antagonists: Y/N (if yes: spironolactone, eplerenone)
- Sacubitril valsartan (Entresto): Y/N

Drugs for treatment of diabetes:
Y/N, If yes: insulin, metformin, sulphonylureas, other – specify

Drugs for the treatment of COPD/asthma (Includes inhalers):
Y/N, If yes: inhaled steroids, inhaled bronchodilators, other – specify

Other prescribed drugs
Specifically ask about regular use of:

- Aspirin: Y/N
- Other anti-platelet agents: Y/N
- NSAIDs: Y/N

- Proton pump inhibitors: Y/N
- H-2 antagonists: Y/N
- Anti-coagulants: Y/N (if yes: warfarin, apixaban, rivaroxaban, dabigatran, edoxaban, other)
- Steroids
- Oral iron
- List any other prescribed drugs patient is regularly taking (free text box)

Over the Counter

Specifically ask about regular use of:

- Aspirin: Y/N
- NSAIDs: Y/N

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 6 weeks can be used including screening bloods):

- Na, K, urea, creatinine, eGFR (MDRD/CKD-EPI)
- 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 six 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

Approximately 15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA. Blood will be centrifuged at 1500g for 20 mins at 4^{o}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, within 2 weeks of study visit 1, and within 6 weeks of randomisation.

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:

Bloods

- Bloods must be collected either during the study visit or in advance of the visit; blood results within 2 weeks of the visit taken as per standard clinical pathways can be used. Results required:
    - Creatinine, eGFR (MDRD/CKD-EPI) – 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 infusion visit (if necessary) to ensure that the infusion can take place.

Medications

- As per baseline but excluding drugs for the treatment of COPD/asthma and other prescribed drugs patient is regularly taking (noted in the free text box at baseline)
- Patients in both arms should be asked regarding use of oral and IV iron.

- Heart Failure medications.
- Treatments for anaemia (including ESA)

Clinical and functional assessment

- systolic and diastolic blood pressure (after 5 minutes rest)
- heart rate (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

A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss).

B) Haemorrhage classified by site and severity
- Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible)
- Severity:- major if both 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).

Bloods

- Bloods must be collected either during the study visit or in advance of the visit; blood results within 3 weeks of the visit taken as per standard clinical pathways can be used. Results required:
  - Creatinine, eGFR (MDRD/CKD-EPI) – 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 infusion visit (if necessary) to ensure that the infusion can take place as planned.

Medication

- As per baseline but excluding drugs for the treatment of COPD/asthma and other prescribed drugs patient is regularly taking (noted in the free text box at baseline)
- Patients in both arms should be asked regarding use of oral and IV iron.
- Heart Failure medications.
- Treatments for anaemia (including ESA)

Clinical and functional assessment

- systolic and diastolic blood pressure (after 5 minutes rest)
- heart rate (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

A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss).

B) Haemorrhage classified by site and severity
   - Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible)

- Severity:- major if both 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 to the visit) must be recorded:

- 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

Approximately 15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA. Blood will be centrifuged at 1500g for 20mins at 4^{o}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.

Note that if a patient's 4 or 20 month visit has taken place remotely during the COVID-19 pandemic, the biobank bloods may be taken at the next available visit (see section 7.8.1). This will be recorded on an 'ad-hoc biobank form' on the eCRF.

7.5.2.5 Final patient visit

The CTU will monitor the accumulation of primary endpoints or other reasons for terminating the trial and will notify sites when to schedule each final patient visit. The final patient visit should take place no later than 4.5 months after the patient's previous visit. The following data should be collected:

Bloods

- Bloods must be collected either during the study visit or in advance of the visit; blood results within 3 weeks of the visit taken as per standard clinical pathways can be used. Results required:
    - Creatinine, eGFR (MDRD/CKD-EPI) – 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 infusion visit (if necessary) to ensure that the infusion can take place as planned.

To evaluate the longer term effects of the IV iron on death and hospitalisations we will be re-dosing those who meet the study criteria and data will be followed up by record linkage (at one and two years in the first instance). This will help understand the legacy from making patients iron replete.

Medications

- As per baseline but excluding drugs for the treatment of COPD/asthma and other prescribed drugs patient is regularly taking (noted in the free text box at baseline)
- Patients in both arms should be asked regarding use of oral and IV iron.
- Heart Failure medications.
- Treatments for anaemia (including ESA)

Clinical and functional assessment

- systolic and diastolic blood pressure (after 5 minutes rest)
- heart rate (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

Serious adverse events

- As well as any recent events, study staff will be asked to confirm that all serious adverse events occurring during the trial have been reported

Study Iron Infusion
Document dose of iron given.

Events of Special Interest

A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss).

B) Haemorrhage classified by site and severity
   - Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible)
   - Severity:- major if both acute and requiring urgent transfusion and minor if not fulfilling these criteria

The patient should also be asked to confirm if they would like to receive a summary of the study results.

7.6 COVID-19

COVID-19 Vaccination

For patients in the IV iron arm of the study, it is recommended that they do not receive the COVID-19 vaccine and their infusion on the same day and if possible, maintain a 7-day interval between the vaccine and infusion in order to avoid incorrect attribution of potential adverse events.

Recording of COVID-19 Vaccinations

Participants should be asked if they have had a COVID-19 vaccine and if they have, the following information should be recorded in the medical notes: how many doses; the name of the vaccine; and approximately when they were given. COVID-19 vaccinations are not recorded on the eCRF, unless they are thought to be related to a serious adverse event, in which case they should be noted in the concomitant medications section of the SAE report.

7.7 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. Note that for this study, non-attendance of study visits is not considered to be a protocol deviation.

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. Where follow-up visits are being conducted remotely, sites will be permitted to post the quality of life questionnaires (EQ-5D and Minnesota Living With Heart Failure) to patients for completion. These questionnaires can also be conducted via telephone.

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.

7.8 Treatment Interruptions and Withdrawal criteria

Withdrawal from study drug

Participants may be withdrawn from the study treatment based on their own preference or based on the clinical judgement of their physician. Any such withdrawals from study treatment will be recorded on the study eCRF with a reason for withdrawal. All such participants will continue to be followed up for clinical events and will be encouraged to attend all study visits.

If participants commence dialysis post-randomisation or are judged to need regular erythropoietin stimulating agents they will be withdrawn from study treatment but continue with follow up as per study protocol.

Participants experiencing severe hypersensitivity to ferric derisomaltose or other parenteral iron products should be withdrawn from the study treatment – see also flow chart (Appendix 2) for handling infusion reactions. The drug causing the hypersensitivity symptoms and the symptoms should be documented.

Postponement or interruptions of IV iron infusion

Postponement or interruptions of IV iron infusion may occur due to the participant's medical condition or other reasons. If there is evidence of significant ongoing infection as judged by the investigator, IV iron infusion should be delayed until the infection has passed or is controlled by antibiotics. Provided this is achieved within 4 weeks of original scheduled visit date then study visit and treatment may be rescheduled as soon as possible. If treatment is delayed for more than 4 weeks due to infection, then the dose is missed with review at next planned study visit.

Postponement of IV iron infusion to a later date should also occur if the participant has decompensated liver cirrhosis (investigator opinion) or active hepatitis (if serum transaminases > 3 x's upper limit of normal). The dose is missed with review at next planned study visit.

Likewise if IV iron infusion is postponed for another reason treatment should continue when clinically indicated. Provided this is achieved within 4 weeks of

original scheduled visit date then study visit and treatment may be rescheduled as soon as possible. If treatment is delayed for more than 4 weeks, then the dose is missed with review at next planned study visit.

Withdrawal from the study

If participants 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. (Non-attendance at study visits is not considered to be a protocol deviation.) Participants will also be consented 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. However, participants will have the right to withdraw consent for further participation and for further data collection. All other participants will be followed up for clinical events until study completion.

Loss of Mental Capacity

If there is a decline in a participant's mental capacity and he/she is no longer able to attend study visits, please note that unless he/she withdraws full consent for further participation then follow up via patient notes and record linkage can still take place; the original consent remains legally valid. This is in keeping with GCP guidelines.

7.9 Storage and analysis of samples

Blood sampling for assay of biomarkers

7.9.1 Sample collection and processing

- Samples will be appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act and the General Data Protection Regulation. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.
- Blood will be collected from patients consenting to participate in the biomarker substudy
- Blood will be taken at baseline, 4 months and 20 months (or next available visit – due to the unprecedented impact of COVID-19 on the delivery of research in 2020 there have inevitably been challenges to see patients face-to-face. Whilst patients may have still had remote study visits, this will have impacted on patients who were due to attend and

have additional samples for biobank. Sites are encouraged to take biobank samples at the next available face-to-face visit.)

- Blood will be collected in pre-chilled sterilins containing EDTA, and centrifuged within 30 minutes at 1500g for 20mins at 4°C. Tubes for sample collection will be sourced by each participating centre and storage tubes will be provided.
- 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.

7.9.2 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.

7.10 End of trial

As this is a morbidity/mortality endpoint driven trial, the end of the trial will be defined to be the date the study endpoints are identified, adjudicated and the database is locked. The study may be stopped prior to the target number of primary endpoints being reached 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 external factors that prevent the target number of events being reached. Once it is anticipated that the desired number of primary endpoints will be achieved or the study is to be terminated for other reasons, final study follow-up dates will be assigned to each participant. This will be done independently of randomised treatment group and of any study data.

8 TRIAL MEDICATION

8.1 Name and description of investigational medicinal product(s)

Ferric derisomaltose (Monofer®)

Monofer® (ferric derisomaltose) is an intravenous (IV) iron compound manufactured by Pharmacosmos A/S (Holbaek, Denmark). Ferric derisomaltose is a complex between iron and a carbohydrate moiety. The carbohydrate moiety is a purely linear chemical structure as shown by ^{13}C nuclear magnetic resonance (NMR) of repeating α-(1-6) linked glucopyranose residues. Thus, it is structurally different from the branched dextran polysaccharides present in iron dextran. The derisomaltose component of ferric derisomaltose consists predominantly of 3-5 glucose units and is prepared from oligomers used for prevention of dextran-induced anaphylactic reaction. These oligomers have been chemically modified to further reduce the potential for anaphylactic/anaphylactoid reaction. Thus, derisomaltose is not a dextran and due to the low anaphylactic potential of ferric derisomaltose there is no requirement for a test dose [19].

The Monofer formulation has strongly bound iron within the iron-carbohydrate complex, which enables a controlled, slow release of bioavailable iron to the iron-binding proteins with only a low risk of free iron toxicity [19]. This allows flexible dosing, including high and rapid dosing.

Following IV administration, ferric derisomaltose is rapidly taken up by the cells in the reticuloendothelial system, particularly in the liver and spleen. Due to its molecular weight it is not eliminated by the kidneys [20].

Monofer® aqueous solution for injection/infusion contains 100mg/ml iron (as ferric derisomaltose). Study sites will be provided with the following:

- Monofer® 5 ml vials containing 500 mg iron as ferric derisomaltose
- Monofer® 10 ml vials containing 1,000 mg iron as ferric derisomaltose

Note: The UK generic name for Monofer changed in 2020 from iron isomaltoside 1000 to ferric derisomaltose to align with the international non-proprietary name (INN). Only the generic name was changed and there was otherwise no change to the medicine or its presentation.

8.2 Legal status of Monofer®

Monofer® (ferric derisomaltose) is currently registered in more than 20 European countries (including UK) and in a number of countries outside Europe. In Europe, ferric derisomaltose is approved for treatment of iron deficiency in patients (either absolute or functional) in whom oral iron administration is unsatisfactory or impossible or where there is a clinical need to deliver iron rapidly.

8.3 Drug storage and supply

Monofer® 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. Monofer® will be supplied by Pharmacosmos UK Ltd and must be stored at a temperature between 5°C and 25°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 ferric derisomaltose

Monofer® 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 more than 15 minutes
- Doses exceeding 1000 mg must be infused over 30 minutes or more

Monofer® 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 Monofer® 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.

Caution should be exercised to avoid paravenous leakage when administrating Monofer®. Paravenous leakage of Monofer® at the injection site may lead to irritation of the skin and potentially long lasting brown discolouration at the site of injection. In case of paravenous leakage, the administration of Monofer® must be stopped immediately.

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 or up to 7 days post randomisation (note: the participant must be present for the randomisation to take place; randomisation cannot be carried out on the web portal in advance of the 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 ferric derisomaltose.

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

There will be no dosage modifications.

8.8 Known drug reactions and interaction with other therapies

Participants with hypersensitivity to the active substance, to ferric derisomaltose, or any of its excipients and/or known serious hypersensitivity to other parenteral iron products are excluded from the trial.

8.9 Concomitant medication

Participants should not receive IV iron if assigned to standard care unless in the opinion of the treating physician it is clinically indicated (for example haemoglobin <9.0 g/dL and evidence of iron deficiency) but may receive oral iron at the discretion

of the treating physicians. No interaction with other concomitant medication is considered likely to confound the results and conclusions. Participants in the IV iron treatment arm should not receive oral iron in combination with their IV iron.

8.10 Trial restrictions

Contraindications will follow the SmPC for Monofer®. Contraception should be used by women with childbearing potential. There is no requirement for contraception for the male participants.

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. Ferric derisomaltose 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

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences that are not necessarily caused by or related to that product. Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and this protocol.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product that is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: 1. results in death 2. is life-threatening 3. requires inpatient hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability/incapacity 5. consists of a congenital anomaly or birth defect

	Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question
Reference Safety Information	The information used for assessing whether an adverse reaction is expected. This is contained in either the investigator's brochure or the summary of product characteristics
Events of Special Interest	A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). B) Haemorrhage classified by site and severity • Site: upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible) • Severity: major if both acute and requiring urgent transfusion and minor if not fulfilling these criteria

*Note: "Severe" is used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 Operational definitions for (S)AEs

IRONMAN is a phase IV trial and the IMP utilised, ferric derisomaltose, has a well understood safety profile and is well tolerated. Data relating to serious adverse events collected within the IRONMAN trial to date (to 28/02/21) indicate that less than 0.13% of SAEs received are considered related to IMP within this patient group.

In addition, participants taking part in this trial are subject to increased levels of hospitalisation due to their diagnosis heart failure. Hospitalisations within the patient group are often for management of the underlying disease, progression of their condition, or due to management of related comorbidities. While these events are important for monitoring participant safety within the trial, they are unlikely to be

related to administration of ferric derisomaltose and are considered anticipated complications.

As such, the pharmacovigilance for this trial will be risk adapted to reflect the demonstrated low level of adverse effects of the IMP on patients. The COVID-19 pandemic has led to the redeployment of some research staff to aid in the management of COVID-19 and urgent public health research. It is therefore vital to minimise the burden of work on local investigators. To ensure that trial sites can focus on the key events and respond to queries from the Sponsor and data management we have simplified the SAE data collection as detailed below.

9.3 Recording of AEs, Events of Special Interest and SAEs in patient's clinical notes

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 attributed to trial medication or not, and should be assessed for seriousness, severity and include the start and stop dates of the event. AEs will be recorded from the date of consent until the end of their trial participation.

Events of special interest as defined below should be recorded within the relevant section of the eCRF; these events are:

- Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss).

- Haemorrhage classified by site and severity
    - Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible)
    - Severity:- major if both acute and requiring urgent transfusion and minor if not fulfilling these criteria

Additional events identified only through record linkage will auto-generate SAE records in the eCRF; however, these should be recorded in the participant's medical records in the same way as AEs.

9.4 Recording of Serious Adverse Events

All Events meeting the criteria of a serious adverse event must be recorded within the eCRF from the time of randomisation until the date of a participants last trial visit +30 days.

The eCRF reporting system will triage SAEs into the relevant category at the time the event is entered onto the system.

All recorded events should be assessed as follows:

Assessment of seriousness

An adverse event is considered serious if it:

1. results in death

2. is life threatening
3. requires hospitalisation or prolongation of existing hospitalisation
4. results in persistent or significant disability or incapacity
5. consists of a congenital anomaly or birth defect
6. is otherwise considered medically significant by the investigator

Assessment of severity

This should be assessed and described using the following categories:

- Mild: awareness of event but easily tolerated
- Moderate: discomfort enough to cause some interference with usual activity
- Severe: inability to carry out usual activity.

The outcome for each event will also be collected and events must be followed up until a resolution is reached.

The timeline for SAE reporting and how these events are assessed is dependent on whether the event is collected for determining study outcomes or for the purposes of pharmacovigilance.

9.4.1 Serious Adverse Events that are Study Outcomes only

While all SAEs are to be recorded within the SAE section of the eCRF, many hospitalisations and deaths reported will be related to the participants underlying cardiovascular disease. These events are important for the analysis of the study endpoints and the monitoring differences in cardiovascular events between arms, but are not considered relevant for the purposes of pharmacovigilance due to their anticipated nature and unlikely relationship to the use of the IMP.

As such, SAEs that occur within participants on the standard care arm and SAEs that occur more than 20 days following administration of IMP for patients on the ferric derisomaltose arm are not subject to expedited review. These events are primarily anticipated events related to the underlying medical condition of the trial participants and will be assessed as potential endpoints by the Endpoint Committee.

Examples of these events are as follows:

- Primary efficacy outcomes
  - Cardiovascular mortality occurring more than 20 days following IMP
  - Hospitalisation for worsening heart failure (both initial and recurrent) occurring more than 20 days following IMP

- Secondary and tertiary efficacy outcomes
  - All-cause mortality (including non-cardiovascular death and death due to undetermined cause) occurring more than 20 days following IMP
  - Hospitalisation for major cardiovascular events occurring more than 20 days following IMP

- Hospitalisation for non-cardiovascular events occurring more than 20 days following IMP

- Safety outcomes
  - Hospitalisation for infection occurring more than 20 days following IMP
  - Mortality due to infection occurring more than 20 days following IMP

In addition to the standard definition of an SAE, all emergency day case treatments for heart failure (e.g. IV infusions of furosemide) or day case/elective admissions for percutaneous coronary intervention or cardiac device insertion should be recorded as SAEs within the eCRF. Under seriousness criteria this should be classified as a 'medically significant event'.

These events must be reviewed by the local investigator and assessed for accuracy and completeness but do not require an assessment of causality and expectedness as they are not considered subject to expedited reporting and review to the Sponsor and REC.

Any change of condition or other follow-up information should be added to the eCRF as soon as it is available

9.4.2 Serious Adverse Events subject to expedited reporting and review

These events are collected for the purposes of monitoring IMP safety; as such they are subject to expedited reporting to the Sponsor and where applicable the MHRA and REC. These events must be reported on the eCRF within 24 hours of local investigators becoming aware of the event.

Reportable events are as follows:

- Any Serious Adverse Event judged by the reporting investigator to have a reasonable possibility of a causal relationship with the IMP irrespective of the period between the administration of IMP and the onset of the event,

- Any Serious Adverse Event occurring within the IMP arm within 20 days of treatment with IMP

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, 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 07989 470505. This must be followed up as soon as possible with an electronic or written report

In addition to the assessments detailed in section 9.4 these events should also be assessed for causality and expectedness by the local investigator as detailed below:

Assessment of causality i.e. does the event have a "reasonable causal relationship" with trial medication. The following categories are used:

- **None:** The event is not considered related to the study drug.
- **Possible:** Although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible.
- **Probable:** The temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug.
- **Definite**: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause.

Assessment of expectedness
If the event is considered to be related (possibly, probably or definitely) to the study medication, an assessment should be made of the expectedness of the reaction i.e. is the reaction a recognised adverse effect of the medication.

The expectedness of an adverse reaction is assessed against the Reference Safety Information (RSI) i.e. the information regarding expected reactions detailed in Section 4.8 (Undesirable effects) of the approved Summary of Product Characteristics for Monofer® 100mg/ml solution for injection/infusion.

- **Expected:** consistent with the relevant product information documented in the RSI.
- **Unexpected:** not consistent with the relevant product information documented in the RSI.

Any event assessed by the local investigators(s) as related to IMP will be assessed for expectedness by the CI/Sponsor against the currently approved RSI. Should a related event be considered unexpected it will be subject to expedited reporting to the MHRA and REC as per section 9.5.

Any change of condition or other follow-up information should be added to the eCRF or 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 an outcome has been reached.

COVID-19 vaccination and reporting

Where a deployed COVID-19 vaccine is suspected to be involved in the onset of a reported event it should be recorded as a concomitant medication. A causal relationship between the vaccine and the event, including potential drug interactions should be assigned by the reporting investigator.

If a reported event is suspected to be due to a deployed COVID-19 vaccine alone reporting investigators should ensure that standard Yellow Card reporting procedures are followed.

9.4.3 Exclusions from the SAE recording and reporting process

The events detailed below do not require reporting as SAEs:

- Routine treatment or monitoring of heart failure not associated with any deterioration in condition
- Treatment which was elective or pre-planned, for a pre-existing non-cardiac condition not associated with any deterioration in condition e.g. pre-planned hip replacement operation which does not lead to further complications
- Any admission to hospital or other institution for general care where there was no deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

9.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any SAE assigned by the PI or delegate and by the CI/Sponsor as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as a SUSAR.

Such events are subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's assessment of causality both opinions will be provided on the report.

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.

9.6 Oversight of events excluded from expedited reporting

SAEs not subject to expedited reporting will be coded and summarised. These events are subject to statistical monitoring and review by the independent data monitoring committee and trial steering committees assigned to the trial. Where potential trends are identified by the IDMC, TSC or statistical monitoring further

events may be considered subject to expedited reporting to the Sponsor and Regulatory authorities.

Where a Serious Adverse Event is initially not subject to Sponsor review but later becomes reportable under sponsor requirements the Date of Sponsor Awareness will be the date there is any indication that the event is linked to administration of IMP. For example, a cardiovascular hospitalisation initially reported as unrelated to IMP that upon further clinical review is considered related to treatment).

9.7 Assessment of Record Linkage reported Serious Adverse Events

Previously unreported SAEs identified via record linkage will be recorded/reported in line with section 9.4.

9.8 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)

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement, confirm seriousness and causality and confirm expectedness of SAEs.
3. Immediate review of all SUSARs and life threatening or fatal SAEs/SARs that begin within 24 hours of IV iron infusion.
4. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).
5. Using definitions in this protocol, confirm events of special interest or potential endpoints

Sponsor:

1. Central data collection and verification of AEs, SAEs, SARs and SUSARs according to the trial protocol
2. Reporting safety information to the CI or delegate for the ongoing assessment of the risk / benefit
3. Assessment and confirmation of expectedness for all reported SARs

4. Reporting safety information to the independent oversight committees identified for the trial (Independent Data Monitoring Committee (IDMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
6. Notifying Investigators of SUSARs that occur within the trial.
7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee:

In accordance with the Charter for the TSC, periodically reviewing recruitment and the overall progress of the trial and liaising with the IDMC and sponsor regarding safety issues.

Independent Data Monitoring Committee:

In accordance with the Charter for the IDMC, periodically reviewing unblinded safety data in individual cases and to determine patterns and trends of events, or identify safety issues, which would not be apparent on an individual case basis, reporting concerns to the TSC and sponsor.

Clinical Endpoint Committee (CEC):

In accordance with the Charter for the CEC, review and classify all potential clinical endpoints in the study.

9.9 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.

9.10 Overdose

Ferric derisomaltose has a low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing.

However, any IMP dose which is not administered in accordance with the protocol should be reported to the sponsor.

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

9.11 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.

9.12 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.

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.

9.13 Development safety update reports

A Development Safety Update Report (DSUR) will be submitted once a year, or on request, to MHRA and REC until the trial is declared ended. The report will be submitted within 60 days of the anniversary of the issue of the Clinical Trials Authorisation for the trial. The DSUR will be prepared by the sponsor (PV Office) in liaison with the CI and Pharmacosmos and submitted by the sponsor (PV Office).

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The original anticipated primary endpoint rate in the control group was 30% in the first year and 60% by three years (median follow-up). Sample size calculations based on recurrent event analyses are complex [21]. Therefore, conservatively, we have based them on a time to first event analysis using the Wald statistic in a Cox

proportional hazards model. We estimated that 570 patients per group (yielding 631 first events) would provide 80% power to detect a hazard ratio of 0.8 (20% reduction in hazard which we believed was 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 intended to recruit 650 patients per group.
In practice, recruitment to IRONMAN has been slower than expected, an issue exacerbated by the COVID-19 pandemic, In addition, event rates have been lower than expected, meaning that the original target number of endpoints would likely not be reached until at least late 2023. The possible need to reconsent patients for longer follow-up and the difficulty in recruiting more patients and retaining existing patients made the target of 631 events unfeasible. Hence, consideration was given to modifying the study objectives.
Since the start of the trial, a meta-analysis of smaller trials of IV iron in heart failure outpatients has suggested a larger treatment effect might be possible (95% CI for the rate ratio in favour of IV iron treatment 0.53 (0.33, 0.86)). Recently, the publication of the AFFIRM-AHF trial that recruited patients after an acute heart failure admission provided, in an analysis adjusting for the COVID-19 pandemic period, a rate ratio (95%CI) in favour of IV iron treatment of 0·75 (0·59, 0·96).
On the basis of this information, the target number of events was recalculated based on a hazard ratio of 0.75, resulting in a new target of 379 events.

10.2 Anticipated recruitment rate

We intend to recruit from up to 100 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

There are no large trials currently recruiting patients with LVEF≤45% or evaluating IV iron on morbidity and mortality in heart failure in the UK. Recruitment will be over a period of around five years.

10.3 Statistical analysis

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 outcome will be analysed using the method of Lin, Wei, Yang & Ying [22] and the data displayed graphically using the method of Ghosh & Lin [23]. In addition, this outcome will be analysed in sensitivity analyses using a joint frailty model for mortality and hospitalisations for worsening heart failure [24] to permit the estimation of the separate effects of treatment on death and heart failure hospitalisation as a recurrent event and also using the Method of Mao and Lin [25]. 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. In the analysis, cardiovascular death will be defined as deaths adjudicated by the endpoint committee as cardiovascular death or as death of undetermined cause.

A primary COVID-19 analysis will be carried out on the primary endpoint and secondary endpoints, in an attempt to minimise the impact of the COVID-19 pandemic. This will include all patients randomised until the end of March 2020 with a censoring date of 30 Sept 2020. Additional sensitivity analysis will be carried involve the use of time varying treatment effects to investigate the impact of the COVID-19 pandemic on the results of the study. Time will be divided into 5 periods; pre first lockdown in the UK, first lockdown until end of first lockdown, end of first lockdown until start of second lockdown, start of second lockdown until end of second lockdown, and end of second lockdown until end of defined patient follow-up.

Full analysis details will be documented in a formal statistical analysis plan that will be completed and signed off before database lock.

10.4 Subgroup analyses

The primary outcome, its sub-components and CV death or hospitalisation for heart failure as a first event will be analysed in the following sub-groups.

Categorical variables: - Sex, recruitment in versus out of hospital, patients taking/not taking hypoglycaemic therapy, TSAT <20% versus ferritin <100ug/L with TSAT ≥20%, aetiology of heart failure, CKD (eGFR <=60 ml/min/1.73m^2) versus no CKD.

Continuously distributed variables: by thirds of the distributions of baseline TSAT, haemoglobin, age, eGFR, systolic blood pressure, LVEF.

Results will be presented within each sub-group along with a test for treatment by sub-group interaction.

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

Unblinded trial data will be reviewed on an ongoing basis by the IDMC. The primary role of the IDMC will be to protect the interests of the patients. The IDMC may recommend to the TSC 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 ~50% and ~70% of the target number of primary endpoints have been adjudicated. 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 TSC/Co-Sponsors.

10.6 Subject population

All analyses will be carried out on an intention to treat basis based on the randomised treatment allocation.

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

The main analyses will be based on morbidity/mortality data for which imputation is not necessary. For quality of life outcomes, laboratory results or other continuous variables, results will be analysed with and without imputation. Multiple imputation procedures will be used for imputation.

10.8 Other statistical considerations.

A Statistical Analysis Plan (SAP) will be maintained as a version controlled document and will be signed off before database lock. The SAP will contain full details of all analyses along with assumptions and procedures for handling problematic or incomplete data (e.g. incomplete dates).

10.9 Economic evaluation

Funding will only be available for an economics evaluation if the study provides a positive result. A health economist has reviewed the protocol to ensure that all relevant data have been collected.

We will collect data on the assumption we will be carrying out a cost-utility analysis, comparing the arms of the study in terms of costs and Quality Adjusted Life Years (QALYs). The main resource use data we will have available will be (1) treatments for iron deficiency in each treatment arm of the study and (2) hospital admissions. In a sensitivity analysis we will test the effect of assuming each hospital admission also involves a follow-up out-patient clinic appointment and two GP consultations.

Hospital admissions will be described using Healthcare Resource Group codes and costed from national tariffs calculated by NHS England. Costs of treating iron deficiency will be calculated from a recognised source of medicines costs such as British National Formulary or MIMS.

QALYs will be calculated by converting EQ-5D scores into utility weights, and estimating area-under-the-curve for patients in each arm of the RCT.

We will calculate the difference in costs and QALYs between the treatment arms and calculate net cost per QALY gained. Costs and QALYs in future years will be discounted and sensitivity analyses will be carried out.

11 DATA HANDLING

11.1 Source Documentation

ICH GCP defines source data as: 'All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial'. In this study, the location of the majority of the source data will be the hospital's medical records including subject case notes, laboratory records and ECGs. The source data transcribed into the eCRF from the medical records must be accurate and verifiable. For questionnaires completed by trial subjects, the completed questionnaires will be regarded as the source data location. In cases where data is transcribed directly into the eCRF and no other paper or electronic source exists, then the eCRF will be considered the source record. In these cases, these data should be prospectively documented in the medical records to ensure a full record of the trial is available at site.

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.

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 NHS Greater Glasgow and Clyde (GG&C) 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 NHS GG&C Research Governance Manager or Lead Clinical Trial Monitor.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (it is noted that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended (this is the Chief Investigator's responsibility).

The Chief Investigator will notify the REC of the end of the study

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

13.2 Peer review

The study protocol has been developed with expert and independent feedback from the Heart Failure Clinical Study Group (British Cardiovascular Society/BHF/NIHR) and the Cardiorenal study group of the UK Kidney Research consortium (UKKRC).

During application for funding from the British Heart Foundation the protocol underwent peer review by 7 independent experts (including heart failure specialists, nephrologists and statisticians). The application for funding the study was approved by the Chairs and Programme Grants Committee of the British Heart Foundation.

13.3 Public and Patient Involvement

Richard Mindham (patient representative on the NICE 2010 Chronic Heart Failure GDG) coordinated input from the West Middlesex patient cardiomyopathy support group. The draft protocol was also reviewed by an independent heart failure service (Gloucestershire – heart failure nurse specialists and patients, coordinated by Head of Specialist Services). 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 patients in the study.

There will be a patient representative on the TSC.

13.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee will apply for NHS permission from the site's Research & Development (R&D) department.

For any amendment that will potentially affect a site's NHS permission, the Chief Investigator/ Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D).

15.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to

enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator, Sponsor and GCTU immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

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

A "serious breach" is a breach which is likely to affect to a significant degree –

1. the safety or physical or mental integrity of the subjects of the trial; or
2. the scientific value of the trial

If any of the above occurs then the CI and Sponsor will be notified. The sponsor will notify the appropriate authorities in writing of any serious breach in accordance with their standard operating procedures.

13.7 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 and the General Data Protection Regulation 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

A log of financial or other competing interests for the CI, PIs and committee members will be held centrally by the Trial Coordinator throughout the trial. The Trial Coordinator will request this information at the site initiation visit and at regular intervals during study conduct, and it will be made available to the Sponsor.

13.9 Indemnity

The Co-Sponsors (University of Glasgow and Greater Glasgow Health Board) 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

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the Sponsor and TSC and any required amendment forms will be submitted to the regulatory authority, ethics committee and Sponsor. The Sponsor will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Following a substantial amendment, favourable opinion/approval must be sought from the original reviewing REC, MHRA (where appropriate) and Research and Development (R&D) office prior to implementation. The Chief Investigator will be responsible for informing the Trial Management Group of all protocol 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

During the trial and in the period prior to publication of the main study results as described in the protocol, only the Glasgow CTU will have access to the full dataset. After that period, the trial Steering Committee will conduct further data analyses for a period of three years. After that time the Trial Steering Committee will consider requests from external parties for further analyses of the study data. Proposals that are scientifically well founded and have an academic basis and where relevant data extractions and analyses are appropriately funded will not be refused. These will be considered as collaborative exercises where the contributions related to study design, conduct, database creation and maintenance and data analysis will be recognised in authorship of any scientific publication. The approach we will take will be to minimise any possibility of breach of participant confidentiality. Normally this will be achieved by minimising data travel. However, for the purposes of individual patient meta-analysis and other reasons, data may be transferred to other sites. Such transfer will require assurances on information security systems at the sites that data are to be transferred to and will involve a legal data transfer agreement. A log of all data requests and subsequent data transfers will be held at the Glasgow CTU.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

The study database will be owned by the University of Glasgow and maintained on behalf of the Study investigators, represented by the Trial Steering Committee as it is constituted during and after the trial.

The study protocol and a description of the recruitment experience and participant baseline characteristics will be published before study completion. On completion of the trial, the database will be locked and analysed by staff of the Robertson Centre for Biostatistics, University of Glasgow. A final study report will be prepared and the results will be published in a major medical journal.

After the main study publications, study investigators will be invited to submit requests for further analyses of the study database. These will be reviewed and prioritised by a Publications Committee made up of the study grant holders and convened by the study co-CIs.
The British Heart Foundation and Pharmacosmos will have the right to see and comment on any results being submitted for publication. A maximum of 28 days will be given for review of major papers and 14 days for abstracts. Such comments will be considered by the Trial Steering Committee.

A lay summary of the main results of the trial will be prepared and provided to all participants via their study site investigators.
Investigators may request a copy of the study data for their participants. Providing some or all of a patient's data to that individual is at their discretion.

14.2 Authorship eligibility guidelines and any intended use of professional writers

The main results of the study will be compiled, written up and published by the study grant holders and others taking responsibility for the study results (e.g. the statistician conducting the final analysis) on behalf of the IRONMAN investigators. The IRONMAN investigators will be listed in an Appendix and will include all site PIs, all committee members and key members of relevant study coordinating groups (including the Sponsor and Glasgow CTU).

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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.

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)

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
IV administration of ferric derisomaltose	Immune: Hypersensitivity/ana-phylactic reactions	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 Cardio-pulmonary resuscitation equipment available at site where administered	Uncommon/Rare	
	Increased risk of infection/oxidative stress	IDMC will specifically receive and review information on infection – related hospitalisations	Rare	

Others?				
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				

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

A guide for managing hypersensitivity reactions which occur during administration of Intravenous (IV) iron.

Administration of IV iron can be complicated by hypersensitivity reactions (HSRs). The European Medicines Agency (EMA) made a statement in 2013 [ref 17], which aims to minimise the risks in box 1. Patients at particular risk of HSRs are listed in box 2. A potential protocol for managing HSRs if they do occur is shown below in Figure 2.

BOX 1 – EMA statement on risks of HSRs to IV iron*

- All IV preparations carry a small risk of reaction and can be life-threatening.
- The benefits of IV iron outweigh the risks when oral iron is inappropriate
- IV iron should only be administered if trained staff and resuscitation is available
- A test dose is not needed
- Patients should be monitored during and for at least 30 minutes after administration infusion.
- **ALL IV iron** is contraindicated in patients with previous serious HSR to any IV iron product
- **NEVER** give IV iron during the first trimester of pregnancy
- Take special care if giving IV iron to patients with known allergies or severe atopy

*European Medicines Agency. New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines. EMA/579491/2013. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500151308.pdf

BOX 2 – Patients at higher risk if given IV iron

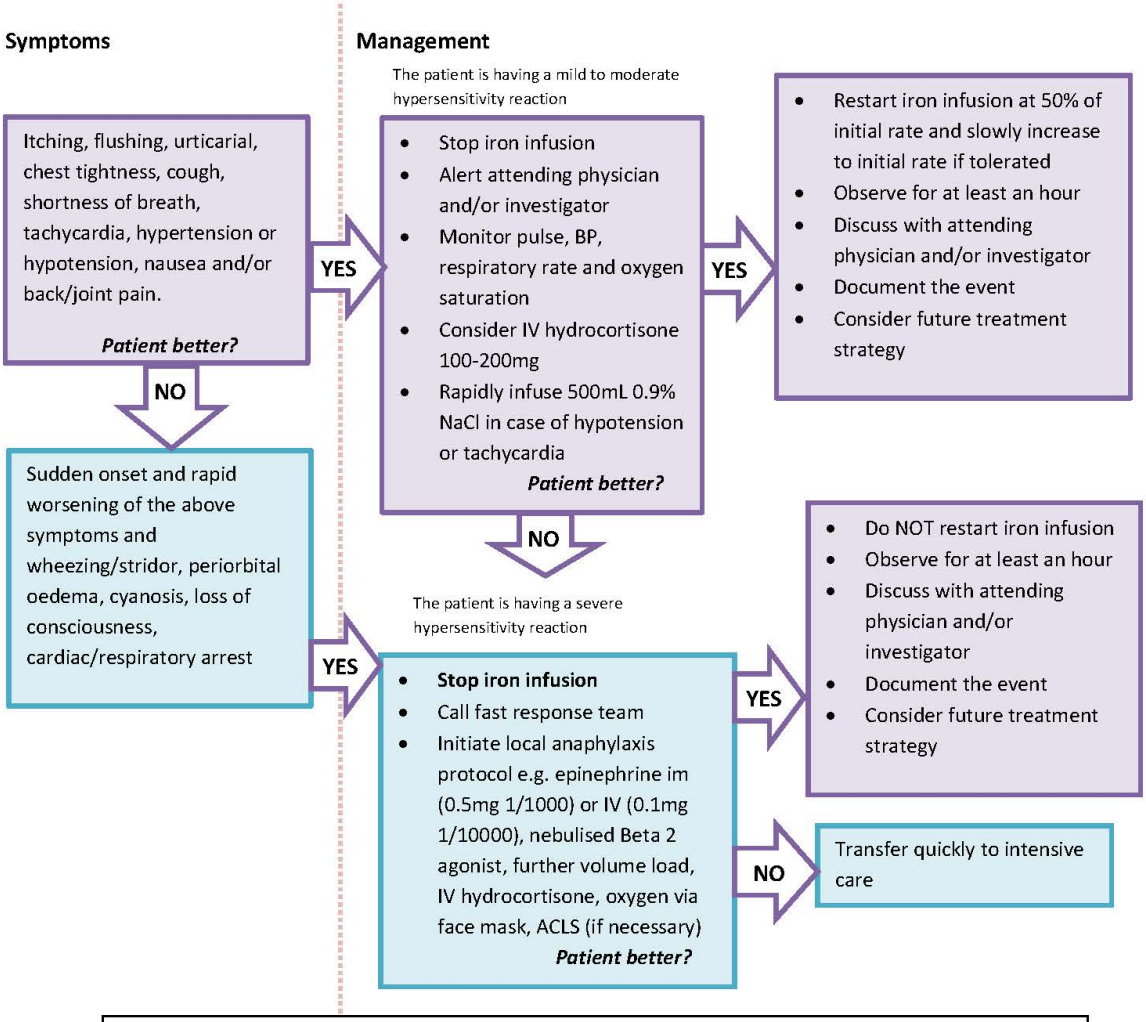
HSR more likely and/or severe

- Previous reaction to IV iron
- Fast infusion rate
- History of drug or other allergies
- Severe asthma of eczema
- Mastocytosis
- Anxiety (patient or staff)

HSR more dangerous

- Severe respiratory or cardiac disease
- Old age
- Beta-blockers, ACE inhibitors
- Pregnancy

Figure 2: Managing HSRs



Adapted from Rampton D, Folkersen J, Fishbane S et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. HAEMATOLOGICA 2014; 99 (11):1671-1676.

16.3 Appendix 3: Contraception

For women of childbearing potential in IRONMAN, acceptable forms of effective contraception include:

1. Established use of oral, injected or implanted hormonal methods of contraception
2. Placement of an intrauterine device (IUD) or intrauterine system (IUS). [Consideration should be given to the type of device or system being used, as there are higher failure rates quoted for certain types, e.g. steel or copper wire]
3. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) – must be combined with spermicidal foam/gel/film/cream/suppository.
4. Sole male partner has been sterilised with appropriate post-vasectomy documentation of the absence of sperm in ejaculate.
5. True abstinence: When this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

16.4 Appendix 4 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
05	2.0	30/05/2017	Dr Paul Kalra	Details of changes can be found in the accompanying document 'IRONMAN protocol v2.0 summary of changes'
06	3.0	09/07/2018	Dr Paul Kalra	Details of changes can be found in the document 'IRONMAN protocol v3.0 summary of changes'
11	4.0	18/09/2019	Dr Paul Kalra	Details of changes can be found in the document 'IRONMAN protocol v4.0 summary of changes'
15	5.0	16/12/2020	Dr Paul Kalra	Details of changes can be found in the document 'IRONMAN protocol v5.0 summary of changes'
19	6.0	15/12/2021	Prof Paul Kalra	Details of changes can be found in the document 'IRONMAN protocol v6.0 summary of changes'

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.

Summary of Protocol Changes

IRONMAN Protocol v2.0 summary of changes

30/05/2017

Protocol page	V1.3 text	V2.0 text	Reason for change
2 (and on footer throughout)	Version 1.3 (11/02/2016)	Version 2.0 (30/05/2017)	Updated
3		ISRCTN16403302 / NCT02642562	ISRCTN and Clinicaltrials.gov numbers inserted (not known at time of previous version)
10	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	5. Physical domain of QoL (Minnesota Living With Heart Failure) – this will be the difference between groups at 4 months and also at 20 months 6. Overall QoL assessment (Minnesota Living With Heart Failure, EQ-5D index and EQ-5D VAS) – this will be the difference between groups at 4 months and also at 20 months	To specify which components of EQ-5D are involved as secondary end point.
10		12. 6 minute walk test - this will be the difference between groups at 4 months and also at 20 months	This was an omission on the original protocol. The 6 minute walk test was always documented as being performed, but not included as a secondary end point.
11	Iron isomaltoside-1000 (100 mg/ml) as an infusion over 15-30 minutes up to a maximum of 20 mg / kg	Iron isomaltoside-1000 (100 mg/ml) administered as an infusion up to a maximum of 20 mg / kg as follows: • Doses up to and including 1000 mg will be	To reflect dosage times as per SPC for Monofer®

		administered over more than 15 minutes • Doses exceeding 1000 mg must be infused over 30 minutes or more	
20	*Trial Flow Chart*	*Trial Flow Chart - updated*	To reflect changes noted elsewhere in protocol
21-23		First infusion may be administered up to 7 days post-randomisation.	To reflect that the infusion may be given on a separate occasion up to 7 days after the randomisation visit. This has been requested by a number of sites to give patients the option of waiting for the iron infusion at the randomisation visit or coming back at a mutually convenient time.
21-23		As the study is event driven, the end of study visit cannot be pre-specified. The number of study visits for a particular patient will depend on both the date of their inclusion in the study and the time when the target number of primary outcomes has been accrued.	Clarification regarding timing of end of study visit.
21-23	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	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 approximately 4.5 years from first randomisation	For consistency within protocol
22	RDW	RDW^	To show RDW is non-mandatory. It has been noted that a number of sites local laboratories do

			not routinely measure this.
23		LVEF assessment[#]	This provides an option for sites to offer an up to date echo as part of assessment towards study entry if the participant is in agreement.
24		9. [#] = If required – an assessment can be carried out if not done in prior 2 years, or most recent result does not permit inclusion	This provides an option for sites to offer an up to date echo as part of assessment towards study entry if the participant is in agreement.
26	It is an investigator designed and initiated study supported by the British Heart Foundation and by an additional grant from Pharmacosmos (the manufacturer of iron isomaltoside which is approved for treating iron deficiency).	It is an investigator designed and initiated study supported by the British Heart Foundation and by an additional grant from Pharmacosmos (the manufacturer of Monofer® which is approved for treating iron deficiency).	To specify that Monofer is being used (there are other formulations of iron isomaltoside).
29	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	5. Physical domain of QoL (Minnesota Living With Heart Failure) – this will be the difference between groups at 4 months and also at 20 months 6. Overall QoL assessment (Minnesota Living With Heart Failure, EQ-5D index and EQ-5D VAS) – this will be the difference between groups at 4 months and also at 20 months	To specify which components of EQ-5D are involved as secondary end point.
29		12. 6 minute walk test - this will be the difference between groups at 4 months and also at 20 months	This was an omission on the original protocol. The 6 minute walk test was always documented as being performed, but not included as a secondary end point.

30	Patient consent for national electronic record linkage in each of the participating countries will be obtained permitting assessment of the impact of the period of randomised treatment on long-term mortality and hospital admission (analysed 2 years after study completion in the first instance).	Patient consent for national electronic record linkage in each of the participating countries will be obtained permitting assessment of events in the year prior to inclusion in the study and impact of the period of randomised treatment on long-term mortality and hospital admission (analysed 2 years after study completion in the first instance).	To note that consent will also be obtained for record linkage for the year leading up to inclusion in the study. This permits the assessment of health care utilisation in the lead up to participants joining the study. This will be of value when analysing the impact of study treatment on outcomes and health economics.
30	The study will be conducted across approximately 50 UK NHS secondary care institutions.	The study will be conducted in up to 100 UK NHS secondary care institutions.	To note that the number of sites taking part may be more than originally stated. There has been considerable interest in the study from more sites than originally anticipated. The involvement of additional sites will help achieve recruitment targets. The study management and monitoring teams are equipped to manage up to 100 sites without compromising quality.
31	2. LVEF <45% within the last 6 months using any conventional imaging modality	2. LVEF ≤45% within the prior two years using any conventional imaging modality	During the first few months of recruitment, it

		(this should be the most recent assessment of LVEF)	has become clear that in routine clinical practice in the UK patients with chronic heart failure are managed on the basis of assessments of left ventricular function (LVEF) that have commonly taken place up to two years previously. This change will ensure that the study population is more representative of patients in routine clinical practice and will thereby make the results more applicable to the general population of patients with heart failure. We believe this change will also benefit the study in terms of recruitment, and that patients will still have higher risk features of heart failure since (i) they are iron deficient, (ii) they are hospitalised (or have recently been) with decompensated heart failure or (iii) they have elevated natriuretic peptides (NT-BNP or BNP).

31	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	5. Any of the following apply: (a) planned cardiac surgery or revascularisation or cardiac device implantation; (b) within 3 months of any of the following: 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), or blood transfusion; (c) on active cardiac transplant list; (d) left ventricular assist device implanted.	1. Reworded for clarification. 2. Within 3 months of device implantation removed. Feedback from sites during the first few months of recruitment has noted that most patients who are being considered for device therapy have very poor left ventricular function. If the trial turns out to be positive in favour of iron infusions then patients would be treated in parallel to consider

			ation for device implantation. As such this proposed change would ensure that the study is closely aligned to clinical practice. Device implantation per se should not impact on the results of the study due to the fact that it is randomised.
31	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	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 investigator's opinion, known or suspected gastro-intestinal malignancy	Missing apostrophe.
32	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	The patient must have LVEF measured within the last two years (this may be done after the patient has consented to the study) and the most recent measure must be ≤45%.	This provides an option for sites to offer an up to date echo as part of assessment towards study entry if the

	undergo formal screening and possible participation in the study.		participant is in agreement.
33	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).	Assessment of LVEF will only be performed specifically for the purposes of this study if the patient has given their consent for the study. Most patients are expected to qualify for this study on the basis of prior measurements of LVEF.	This provides an option for sites to offer an up to date echo as part of assessment towards study entry if the participant is in agreement.
34	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.	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. All patients will have at least 24 hours to review the patient information sheet before being approached for consent. 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.	To reiterate that patients will have at least 24 hours to review the patient information sheet.
35	Randomisation will be achieved by accessing a web based randomisation system (with a telephone interactive voice response system as alternative).	Randomisation will be achieved by accessing a web based randomisation system.	There is no interactive voice response system for IRONMAN.
35	• Duration of heart failure: specify - new diagnosis, < 1 year, > 1 year (and specify number of years)	• Duration of heart failure: specify - new diagnosis, < 1 year, >= 1 year (and specify number of years)	Correction to >= 1 year
37	• MCV, MCHC, MCH, RDW	• MCV, MCHC, MCH, RDW*	To show RDW is non-mandatory. It has been noted that a number of sites local laboratories do not routinely measure this.

39	15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA and aprotonin.	Approximately 15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA.	To clarify amount collected is approximate, and that the sterilins should contain EDTA only.
41	Medications • As per baseline but patients in both arms should be asked regarding use of oral and IV iron. • Heart Failure medications. • Treatments for anaemia (including ESA)	Medications • As per baseline but excluding drugs for the treatment of COPD/asthma and other prescribed drugs patient is regularly taking (noted in the free text box at baseline) • Patients in both arms should be asked regarding use of oral and IV iron. • Heart Failure medications. • Treatments for anaemia (including ESA)	To simplify the data collected at each visit to that essential for the study.
41	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.	Events of Special Interest A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). B) Haemorrhage classified by site and severity • Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible) • Severity:- major if both acute and requiring urgent transfusion and minor	Reworded for clarity.

		if not fulfilling these criteria	
42	Medication • As per baseline but patients in both arms should be asked regarding use of oral and IV iron. • Heart Failure medications. • Treatments for anaemia (including ESA)	Medication • As per baseline but excluding drugs for the treatment of COPD/asthma and other prescribed drugs patient is regularly taking (noted in the free text box at baseline) • Patients in both arms should be asked regarding use of oral and IV iron. • Heart Failure medications. • Treatments for anaemia (including ESA)	To simplify the data collected at each visit to that essential for the study.
43	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.	Events of Special Interest A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). B) Haemorrhage classified by site and severity • Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible) • Severity:- major if both acute and requiring urgent transfusion and minor if not fulfilling	Reworded for clarity.

		these criteria	
43	• MCV, MCHC, MCH, RDW	• MCV, MCHC, MCH, RDW*	To show RDW is non-mandatory. It has been noted that a number of sites local laboratories do not routinely measure this.
43	15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA and aprotonin.	Approximately 15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA.	To clarify amount collected is approximate, and that the sterilins should contain EDTA only.
44	*LPLV is expected to be 4years and 4 months from first randomisation.*	*LPLV is expected to be approximately 4.5 years from first randomisation.*	For consistency within protocol.
44	Medications • As per baseline but patients in both arms should be asked regarding use of oral and IV iron. • Heart Failure medications. • Treatments for anaemia (including ESA)	Medication • As per baseline but excluding drugs for the treatment of COPD/asthma and other prescribed drugs patient is regularly taking (noted in the free text box at baseline) • Patients in both arms should be asked regarding use of oral and IV iron. • Heart Failure medications. • Treatments for anaemia (including ESA)	To simplify the data collected at each visit to that essential for the study.
44	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	Events of Special Interest A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). B) Haemorrhage classified by site and severity • Site:- upper GI, lower GI, genitourinary (GU),	Reworded for clarity.

	and minor if not fulfilling these criteria.	Other (note – bleeding from more than one site is possible) • Severity:- major if both acute and requiring urgent transfusion and minor if not fulfilling these criteria	
46	Blood will be collected in pre-chilled sterilins containing EDTA and aprotonin, and centrifuged within 30 minutes at 1500g for 20mins at 4oC. Tubes for sample collection and storage will be sourced by each participating centre.	Blood will be collected in pre-chilled sterilins containing EDTA, and centrifuged within 30 minutes at 1500g for 20mins at 4oC. Tubes for sample collection will be sourced by each participating centre and storage tubes will be provided.	To confirm that the sterilins should contain EDTA only. Tubes for storage will be provided to the sites but tubes for collection will need to be sourced locally.
47	Iron (III) isomaltoside 1000 is an intravenous (IV) iron compound manufactured by Pharmacosmos A/S (Holbaek, Denmark).	Monofer® (Iron (III) isomaltoside 1000) is an intravenous (IV) iron compound manufactured by Pharmacosmos A/S (Holbaek, Denmark).	To specify that Monofer is being used.
48	8.2 Legal status of iron (III) isomaltoside 1000 Iron isomaltoside 1000 is currently registered in more than 20 European countries (including UK) and in a number of countries outside Europe.	8.2 Legal status of Monofer® Monofer® (Iron isomaltoside 1000) is currently registered in more than 20 European countries (including UK) and in a number of countries outside Europe.	To specify that Monofer is being used.
48	Monofer® will be distributed by Pharmacosmos UK Ltd and must be stored at a temperature between 2°C and 30°C.	Monofer® will be supplied by Pharmacosmos UK Ltd and must be stored at a temperature between 5°C and 25°C.	Monofer is supplied by Pharmacosmos but is now distributed by another company.

			Correction to storage temperature range.
49	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	The rate of infusion is dependent on the dose as follows: • Doses up to and including 1000mg must be infused over more than 15 minutes • Doses exceeding 1000 mg must be infused over 30 minutes or more	To reflect dosage times as per SPC for Monofer®
49	All participants in the treatment arm will receive an infusion at the randomisation visit.	All participants in the treatment arm will receive an infusion at the randomisation visit or up to 7 days post randomisation (note: the participant must be present for the randomisation to take place; randomisation cannot be carried out on the web portal in advance of the visit).	To allow for the infusion to be given up to 7 days after randomisation (some sites have reported difficulty with getting time/location for infusion at short notice so this would allow infusions to be scheduled in advance). To highlight that randomisation must not be carried out on the web portal in advance of the randomisation visit.
52	The following SAEs, which are also efficacy outcome measures, will be recorded in the eCRF but excluded from immediate reporting to the sponsor: • Cardiovascular mortality • Cardiovascular hospitalisation (including hospitalisations for CV events or hospitalisation during which a CV event occurs). A	The following SAEs, which are also efficacy outcome measures, will be recorded in the eCRF but excluded from immediate reporting to the sponsor if thought to be unrelated to the trial treatment or the event occurs more than 30 days post cessation of trial treatment: • Cardiovascular mortality	To clarify that events classifying as both efficacy outcomes and serious adverse events are subject to immediate reporting, and that events classified as efficacy outcomes only are not subject

	cardiovascular admission will be taken to be any admission that does not have a clear non-cardiovascular cause. Cardiovascular death and cardiovascular hospitalisation would be considered to be expected in the trial population and therefore will be excluded from immediate reporting to the sponsor unless also considered to be related to the trial medication.	• Cardiovascular hospitalisation (including hospitalisations for CV events or hospitalisation during which a CV event occurs). A cardiovascular admission will be taken to be any admission that does not have a clear non-cardiovascular cause. Cardiovascular deaths and cardiovascular hospitalisations considered to be related to trial treatment and occurring within 30 days of trial treatment are subject to immediate reporting to the sponsor as per section 9.3.1.	to regulatory timelines.
53	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.	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. AEs will be recorded from consent until the later of 30 days post cessation of trial treatment or the end of the study. All Events of Special Interest, SAEs and SUSARs will be recorded in the participant's medical records and on the eCRF, and will be recorded from the point of randomisation until the later of 30 days post cessation of trial treatment or the end of the study. Additional events identified only through record linkage will generate SAE records in the eCRF, and should be recorded in the participant's	Removal of CAPS in title. To clarify reporting requirements for AEs/Events of Special Interest/SAEs and SUSARs. To note that record linkage events will produce SAEs in the eCRF, and should be recorded in the participant's medical records.

		medical records in the same way as AEs.	
53	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.	Events of Special Interest A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). B) Haemorrhage classified by site and severity • Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible) • Severity:- major if both acute and requiring urgent transfusion and minor if not fulfilling these criteria	Reworded for clarity.
54	Serious Adverse Events (SAE)	9.3.1 Site Reported Serious Adverse Events (SAE)	Numbering of section and clarification that it concerns site reported SAEs only.
56		9.3.2 Record Linkage Reported Serious Adverse Events Previously unreported SAEs identified via record linkage will be reviewed and assessed for relatedness and expectedness by the Chief	Section added to describe the process of review for SAEs identified initially by record linkage.

		Investigator or his designee. The PI and/or designee will be notified when additional SAEs have been created in the system from record linkage.	
56	Reporting to sponsor	9.3.3 Reporting to sponsor	Numbering of section
56	Suspected Unexpected Serious Adverse Reactions (SUSARs)	9.3.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)	Numbering of section
56	Any SAE assigned by the PI or delegate and by the CI (on behalf of the sponsor), as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as SUSAR and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment both opinions will be provided on the report.	Any SAE assigned by the PI or delegate and by the CI (on behalf of the sponsor) or by the CI or designee in the case of events identified only by record linkage, as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as a SUSAR and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment both opinions will be provided on the report.	To clarify that the CI or designee would assign relatedness and expectedness in the case of record linkage events.
57	2. Using medical judgement, confirm seriousness and causality and assign expectedness of SAEs.	2. Using medical judgement, confirm seriousness and causality and confirm expectedness of SAEs.	The CI will confirm after the PI has assigned expectedness
57	3. Immediate review of all SUSARs.	3. Immediate review of all SUSARs and life threatening or fatal SAEs/SARs that begin within 24 hours of IV iron infusion.	To ensure CI is aware of serious events that have occurred.
58	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	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	Missing close bracket added.

	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	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.	
58	However any overdose of the IMP should be documented as a protocol deviation and reported to the sponsor.	However any IMP dose which is not administered in accordance with the protocol should be reported to the sponsor.	For clarification
60	There are no large trials currently recruiting patients with LVEF≤45% or evaluating IV iron on morbidity and mortality in heart failure.	There are no large trials currently recruiting patients with LVEF≤45% or evaluating IV iron on morbidity and mortality in heart failure.	For consistency within protocol.
63	Paper worksheets which represent the eCRF content will be available to facilitate data capture at the study sites.		Paper worksheets are not provided by Sponsor.
74		Appendix 4 – amendment history	Updated with details of protocol v2.0.

Protocol page	V2.0 text	V3.0 text	Reason for change
2 (and on footer throughout)	Version 2.0 (30/05/2017)	Version 3.0 (09/07/2018)	Updated
7	callum.chapman@wmuh.nhs.uk	Callum.Chapman@chelwest.nhs.uk	Updated contact detail
20	*Trial Flow Chart*	*Trial Flow Chart - updated*	To reflect changes noted elsewhere in protocol
21-23	For other participants randomisation should occur within 2 weeks of screening blood tests.	For all participants, screening and randomisation must be completed using blood tests within 6 weeks of the respective visit.	In the previous protocol clinically available bloods that were available within 4 weeks could be used for screening, whilst these needed to be within 2 weeks for randomisation. Many sites have highlighted that this meant that there was often a need for patients to be re-bled at screening to ensure bloods were available within 2 weeks for randomisation. This was felt to be inconvenient for patients and staff. The Trial Steering Committee felt that in clinical practice, if intravenous iron is proven to be of clinical benefit, then it is reasonable to prescribe intravenous iron based on blood tests within 6 weeks. This fits with current clinical practice in other disease areas. In addition, when considering safety, all

Protocol page	V2.0 text	V3.0 text	Reason for change
			patients are asked prior to the administration of intravenous iron whether they have had any iron product (IV or oral) since the last visit.
24	5. ^^ = use values from assessments within 2 weeks of randomisation if available	5. ^^ = use values from assessments within 6 weeks of randomisation if available	See point above
31	*Inclusion criteria* 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	*Inclusion criteria* 5. Evidence of being in a higher risk HF group: 1. Current (with the expectation that patient will survive to discharge) or recent (within 6 months) hospitalisation for HF	Feedback from sites highlighted that the previous terminology 'intention to discharge in the next 48 hours' has been a hindrance to recruiting patients hospitalised for heart failure. This is due to the fact that discharge dates are often not predictable, and it is common practice for patients to be transferred from intravenous diuretic infusions to oral tablets and then be discharged within 24 hours. The aim of the original terminology was to try to avoid approaching and recruiting patients who were so sick that they might not survive to hospital discharge (data from the National Heart Failure audit suggest that in hospital mortality is just below 10%). The Trial Steering Committee agreed that the

Protocol page	V2.0 text	V3.0 text	Reason for change
			suggested change to wording would be easier for sites to follow and remove concern that if a patient e.g. went home in 72 hours as opposed to within 48 hours that it might constitute a protocol deviation.
31	*Exclusion criteria* 3. Chronic defined need for IV iron therapy	*Exclusion criteria* 3. Already planned to receive IV iron	'Chronic defined need for IV iron' has been highlighted as by sites as being vague. As such we felt this change would be much clearer – if a patient is 'already planned to receive IV iron' they should be excluded from the study.
31	*Exclusion criteria* 5. Any of the following apply: (a) planned cardiac surgery or revascularisation or cardiac device implantation;	*Exclusion criteria* 5. Any of the following apply: (a) planned cardiac surgery or revascularisation;	This had been planned to be removed at the last protocol amendment but was left in by mistake. We justified this last time since feedback from sites during the first few months of recruitment noted that most patients who are being considered for device therapy have very poor left ventricular function. If the trial turns out to be positive in favour of iron infusions then patients would be treated in parallel to consideration for device implantation. As such this proposed change would ensure that the study is

Protocol page	V2.0 text	V3.0 text	Reason for change
			closely aligned to clinical practice. Device implantation per se should not impact on the results of the study due to the fact that it is randomised.
31	*Exclusion criteria* 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	*Exclusion criteria* 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 disease.	Changed to be in keeping with current Summary of Product Characteristics for Monofer.
33	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	The majority of patients will have contemporary blood investigations. For screening purposes haemoglobin and eGFR assessed for clinical purposes within the last 6 weeks will be used	See note for page 21-23
33	Formal screening for eligibility specific to the three settings, assuming the other inclusion and exclusion criteria (section 6) are met (clinical bloods	Formal screening for eligibility specific to the three settings, assuming the other inclusion and exclusion criteria (section 6) are met (clinical bloods	See note for page 21-23

Protocol page	V2.0 text	V3.0 text	Reason for change
	taken in the last 4 weeks will be used if available)	taken in the last 6 weeks will be used if available)	
34		**7.1.4 Re-screening post-consent** Patients may fail screening post-consent, due to one or more blood results falling outside the study parameters. In these circumstances, re-testing of bloods will be permitted once for each patient. If the initial consent was signed within 2 months of the re-testing, new consent is not required unless the consent form template has been updated in this period. If the initial consent was not signed within 2 months of re-testing then consent should be sought again. Patients should keep the same 5-digit Patient ID and the data should be amended on the web portal as appropriate. Note that, if applicable, the new consent form will need to be scanned and uploaded to the secure study database.	Investigators have fed back that a proportion of patients who have consented to IRONMAN are excluded due to having a blood parameter that doesn't quite meet the inclusion criteria (or has become an exclusion) despite all other criteria being met. For some patients it is reasonable, assuming they are happy, to re-screen with repeated blood tests. This suggested amendment is designed to clarify this. It was felt that if this occurred after more than 2 months from original consent the patient should be re-consented.
34	**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.	**7.1.5 Randomisation** Patients who are being randomised will be required to have undergone screening and have recent blood tests available from within the previous six weeks.	Section renumbered due to addition of re-screening section. See note for page 21-23
36	• LVEF: when – date off assessment	• LVEF: when – date of assessment	Correction to spelling.
36	• Duration of heart failure: specify - new diagnosis, < 1 year, >= 1 year (and specify number of years)	• Duration of heart failure: specify - new diagnosis, <= 1 year, >1 year (and specify number of years)	Correction to categories (to match eCRF response options).

Protocol page	V2.0 text	V3.0 text	Reason for change
37	• Entresto (LCZ 696): Y/N	• Sacubitril valsartan (Entresto): Y/N	To include the generic name for this medication.
37	**7.4.5 Baseline blood parameters (blood tests within 2 weeks can be used including screening bloods):**	**7.4.5 Baseline blood parameters (blood tests within 6 weeks can be used including screening bloods):**	See note for page 21-23
38	• MCV, MCHC, MCH, RDW*	• MCV, MCHC, MCH • RDW*	RDW moved to new line to clarify that it is the only one of the four that is not mandated.
38	Prior to randomisation all patients require to have had blood results within the last two weeks.	Prior to randomisation all patients require to have had blood results within the last six weeks.	See note for page 21-23
40	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.	In order to use these results for the study these would need to be available within 3 weeks of study visits 2-13, within 2 weeks of study visit 1, and within 6 weeks of randomisation.	See note for page 21-23
41	• heart rate and rhythm (after 5 minutes rest)	• heart rate (after 5 minutes rest)	It is purely heart rate that is being assessed on these visits and not rhythm.
43	• heart rate and rhythm (after 5 minutes rest)	• heart rate (after 5 minutes rest)	It is purely heart rate that is being assessed on these visits and not rhythm.
43	• MCV, MCHC, MCH, RDW*	• MCV, MCHC, MCH • RDW*	RDW moved to new line to clarify that it is the only one of the four that is not mandated.
44	• heart rate and rhythm (after 5 minutes rest)	• heart rate (after 5 minutes rest)	It is purely heart rate that is being assessed on these visits and not rhythm.
48	• Monofer® 1 ml vials containing 100 mg iron as iron (III) isomaltoside 1000		Sites will no longer be provided with the 1ml vials as these are not required.
49		Caution should be exercised to avoid paravenous leakage	Changed to be in keeping with current

Protocol page	V2.0 text	V3.0 text	Reason for change
		when administrating Monofer. Paravenous leakage of Monofer at the injection site may lead to irritation of the skin and potentially long lasting brown discolouration at the site of injection. In case of paravenous leakage, the administration of Monofer must be stopped immediately.	Summary of Product Characteristics for Monofer.
52	**9.2 Operational definitions for (S)AEs** Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and this protocol. All Serious Adverse Events (SAEs) occurring during the trial will be recorded in the eCRF. Hospitalisation for the following reasons will not be considered to be SAEs: • Routine treatment or monitoring of heart failure not associated with any deterioration in condition. • Treatment which was elective or pre-planned, for a pre-existing non-cardiac condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications. • Any admission to hospital or other institution for general care	**9.2 Operational definitions for (S)AEs** Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and this protocol. IRONMAN is a phase IV trial, and the iron (III) Monofer® isomaltoside as IMP has a well understood safety profile and is well tolerated. Data relating to serious adverse events collected within the IRONMAN trial so far indicate that 1.5% of SAEs received (prior to 28/02/18) are considered related to the administration of IMP within this patient group. As such, and taking into account the increased levels of hospitalisation for cardiovascular morbidity within IRONMAN participants, the following process will be followed for all SAEs. All Serious Adverse Events (SAEs) occurring during the trial will be recorded within the eCRF. However, the following serious adverse events that are also efficacy outcome measures are to be excluded from reporting to the Sponsor	The initial protocol aimed to exclude expected cardiovascular events from reporting to sponsor. These amendments clarify that the only events to be reportable are those thought to be due to IMP or non cardiovascular in nature. Given the high level of hospitalisations for cardiovascular morbidity/mortality within the patient group, and the well understood safety profile of the IMP by collecting only SARs and non cardiovascular SAEs the level of pharmacovigilance can be reduced with no additional risk to the patients or the trial integrity. The need to assign causality and expectedness for SAEs occurring in patients on the standard care arm has also been removed. As the patient does not

Protocol page	V2.0 text	V3.0 text	Reason for change
	where there was no deterioration in condition. • Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission. For the avoidance of doubt, all emergency day case treatments for heart failure or involving percutaneous coronary intervention or cardiac device insertion should be included. The following SAEs, which are also efficacy outcome measures, will be recorded in the eCRF but excluded from immediate reporting to the sponsor if thought to be unrelated to the trial treatment or the event occurs more than 30 days post cessation of trial treatment: • Cardiovascular mortality • Cardiovascular hospitalisation (including hospitalisations for CV events or hospitalisation during which a CV event occurs). A cardiovascular admission will be taken to be any admission that does not have a clear non-cardiovascular cause. Cardiovascular deaths and cardiovascular hospitalisations considered to be related to trial treatment and	PV Office, as they are considered expected events within this participant population • Cardiovascular mortality • Cardiovascular hospitalisation (including hospitalisations for CV events or hospitalisation during which a CV event occurs). A cardiovascular admission will be taken to be any admission that does not have a clear non-cardiovascular cause. • All Serious Adverse Events occurring in participants within the standard care arm as there is no IMP exposure within this participant group. All Serious Adverse Events will be subject to review by the Principal Investigator or an authorised clinician. Serious adverse events meeting the following criteria will be subject to expedited review by the PV Office following clinical review: • Any Serious Adverse Event considered related to trial treatment occurring within 30 days of treatment with the IMP; including any cardiovascular deaths or hospitalisations considered related to IMP administration. • Any Serious Adverse Event occurring within the IMP arm not considered to be a cardiovascular hospitalisation or cardiovascular death and occurring within 30 days of treatment with IMP. For the purposes of the PV Office the date of Sponsor	receive IMP then SAEs occurring in this arm are not considered reportable to sponsor. Cardiovascular events unrelated to IMP, and events occurring within the standard care arm will still be captured and will be assessed by the DMC.

Protocol page	V2.0 text	V3.0 text	Reason for change
	occurring within 30 days of trial treatment are subject to immediate reporting to the sponsor as per section 9.3.1. If related to the trial medication these would not be considered to be SUSARs unless the severity of the event was considered to be unexpected.	awareness of an SAE will be considered the date there is any indication the event is linked to the administration of IMP. <u>Exclusions from SAE reporting</u> Hospitalisation for the following reasons will not be considered to be SAEs: • Routine treatment or monitoring of heart failure not associated with any deterioration in condition. • Treatment which was elective or pre-planned, for a pre-existing non-cardiac condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications. • Any admission to hospital or other institution for general care where there was no deterioration in condition. • Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission. For the avoidance of doubt, all emergency day case treatments for heart failure or involving percutaneous coronary intervention or cardiac device insertion should be included.	
56		**For participants on the standard care arm, no assessment of causality is required as patients do not receive trial IMP.**	The study is open labelled and hence those receiving standard care alone do not receive IMP.
56		**For participants on the standard care arm, no assessment of expectedness is**	The study is open labelled and hence those receiving

<table>
<tr><th>Protocol page</th><th>V2.0 text</th><th>V3.0 text</th><th>Reason for change</th></tr>
<tr><td></td><td></td><td>required as patients do not receive trial IMP.</td><td>standard care alone do not receive IMP.</td></tr>
<tr><td>57</td><td>9.3.3 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.</td><td>9.3.3 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 upon any indication that the event is considered related to the IMP.</td><td>In order to ensure that we fully capture serious adverse events thought to be due to the IMP events will be submitted to the sponsor PV office where sites suspect that there is a link between IMP and the event. This is a further clarification of the information detailed in section 9.2.</td></tr>
<tr><td>71</td><td><table><tr><th>Activity</th><th>Frequency</th></tr><tr><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></tr></table></td><td><table><tr><th>Activity</th><th>Frequency</th></tr><tr><td>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

Cardio-pulmonary resuscitation equipment available at site where administered</td><td>

Uncommon/ Rare</td></tr></table></td><td>Updated SmPC has hypersensitivity as uncommon but anaphylactoid/anaphylactic reactions as rare. Text reordered so that hazards, activity, and frequency align.</td></tr>
<tr><td>76</td><td></td><td>Appendix 4 – Amendment History</td><td>Updated with details of protocol v3.0</td></tr>
</table>

IRONMAN Protocol v4.0 summary of changes

18/09/2019

Protocol page	V3.0 text	V4.0 text	Reason for change
2 (and on footer throughout)	Version 3.0 (09/07/2018)	Version 4.0 (18/09/2019)	Updated
6		Project Manager – Lizzie Thomson Email : Elizabeth.Thomson@glasgow.ac.uk	To add Project Manager's details to protocol.
6	NHS Greater Glasgow & Clyde Research and Development Management Office West Glasgow Ambulatory Care Hospital Dalnair Street Glasgow G3 8SJ Contact: Dr Maureen Travers Tel: 0141 232 1813 E-mail:maureen.travers@ggc.scot.nhs.uk	NHS Greater Glasgow & Clyde Research and Development Ward 11, Dykebar Hospital Grahamston Road Paisley PA2 7DE Contact: Dr Maureen Travers Tel: 0141 314 4012 E-mail: maureen.travers@ggc.scot.nhs.uk	Change to sponsor contact details.
8	Dr Elizabeth Douglas MRPharmS Clinical Trials Pharmacist Research and Development Management Office West Glasgow Ambulatory Care Hospital Dalnair Street Glasgow G3 8SJ Tel: 0141 232 1792 E-mail: elizabeth.douglas@ggc.scot.nhs.uk	Dr Elizabeth Douglas MRPharmS Clinical Trials Pharmacist R&D Pharmacy Team Research and Development Ward 11, Dykebar Hospital Grahamston Road Paisley PA2 7DE Tel: 0141 314 4083 E-mail: elizabeth.douglas@ggc.scot.nhs.uk	Change to trials pharmacist contact details.
10	SECONDARY SAFETY 1. Death due to sepsis	SECONDARY SAFETY 1. Death due to infection	Felt to be a more appropriate term and maintains

Protocol page	V3.0 text	V4.0 text	Reason for change
			consistency in protocol.
16	*Contents page*	*Contents page – updated*	To reflect page number changes
17		CKD-EPI Chronic Kidney Disease Epidemiology Collaboration	Added to List of Abbreviations as now used within protocol.
20	*Trial Flow Chart*	*Trial Flow Chart - updated*	To reflect changes noted elsewhere in protocol
29	SECONDARY SAFETY 1. Death due to sepsis	SECONDARY SAFETY 1. Death due to infection	As above
31	*Exclusion criteria* 2. MDRD estimated glomerular filtration rate (eGFR) <15ml/min/1.73m^2	*Exclusion criteria* 2. MDRD/CKD-EPI estimated glomerular filtration rate (eGFR) <15ml/min/1.73m^2	Many laboratories now routinely report eGFR with CKD-EPI formula (some still report eGFR according to MDRD formula). Both are validated and acceptable for clinical decision making. Hence this means that investigators can use local lab data.
35	Heart failure: • Aetiology (ischaemic, dilated cardiomyopathy, hypertension, valve disease, other – specify, unknown)	Heart failure: • Aetiology (ischaemic, dilated cardiomyopathy, hypertension, valve disease, congenital, other – specify, unknown)	Patients with heart failure secondary to congenital heart disease can be included.
37	• Na, K, urea, creatinine, eGFR (MDRD)	• Na, K, urea, creatinine, eGFR (MDRD/CKD-EPI)	As above
41	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	The following will be documented/undertaken: Bloods • Bloods must be collected either during the study visit or in advance of the visit; blood results within 2	This gives sites the option of obtaining blood results prior to the specific study visit or taking them on

Protocol page	V3.0 text	V4.0 text	Reason for change
	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.	weeks of the visit taken as per standard clinical pathways can be used. Results required: • Creatinine, eGFR (MDRD/CKD-EPI) – 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 infusion visit (if necessary) to ensure that the infusion can take place.	the day of the visit. This permits greater flexibility for patients to ensure the most convenient strategy is followed.
42	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.	Bloods • Bloods must be collected either during the study visit or in advance of the visit; blood results within 3 weeks of the visit taken as per standard clinical pathways can be used. Results required: • Creatinine, eGFR (MDRD/CKD-EPI) – 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 infusion visit (if necessary) to ensure that the infusion can take place as planned.	As above

Protocol page	V3.0 text	V4.0 text	Reason for change
44	Blood parameters (either taken at the visit or within the 3 weeks prior visit) must be available prior to the visit:	Blood parameters (either taken at the visit or within the 3 weeks prior to the visit) must be recorded:	As above
44	platelets	Platelets	Grammatical correction
45	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 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. Note that for this study, non-attendance of study visits is not considered to be a protocol deviation.	It has been noted elsewhere in the protocol that patients' health may change as the study progresses. For example, if they become more frail and find it difficult to attend all visits then this should be managed as best as possible to ensure as much data as possible is recorded without patients feeling pressured to attend.
46	If participants 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.	If participants 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. (Non-attendance at study visits is not considered to be a protocol deviation.)	It has been noted elsewhere in the protocol that patients' health may change as the study progresses. For example, if they become more frail and find it difficult to attend all visits then this should be managed as best as possible to ensure as much data as

Protocol page	V3.0 text	V4.0 text	Reason for change
			possible is recorded without patients feeling pressured to attend.
47		Loss of Mental Capacity If there is a decline in a participant's mental capacity and he/she is no longer able to attend study visits, please note that unless he/she withdraws full consent for further participation then follow up via patient notes and record linkage can still take place; the original consent remains legally valid. This is in keeping with GCP guidelines.	Clarification regarding follow up for patients who lose mental capacity during the study.
52	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and this protocol.	Moved from the beginning of section 9.2 as better to highlight in the definitions section.
53		Events of Special Interest A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). B) Haemorrhage classified by site and severity • Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible) • Severity:- major if both acute and requiring urgent	Added to definitions section for clarity.

Protocol page	V3.0 text	V4.0 text	Reason for change
		transfusion and minor if not fulfilling these criteria	
53	**9.2 Operational definitions for (S)AEs** Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and this protocol.		Moved to section 9.1 (definitions).
53	IRONMAN is a phase IV trial, and the iron (III) Monofer® isomaltoside as IMP has a well understood safety profile and is well tolerated. Data relating to serious adverse events collected within the IRONMAN trial so far indicate that 1.5% of SAEs received (prior to 28/02/18) are considered related to the administration of IMP within this patient group. As such, and taking into account the increased levels of hospitalisation for cardiovascular morbidity within IRONMAN participants, the following process will be followed for all SAEs. All Serious Adverse Events (SAEs) occurring during the trial will be recorded within the eCRF. However, the following serious adverse events that are also efficacy outcome measures are to be excluded from reporting to the Sponsor PV Office, as they are considered expected events within this participant population • Cardiovascular mortality • Cardiovascular hospitalisation (including hospitalisations for CV	IRONMAN is a phase IV trial, and the iron (III) Monofer® isomaltoside as IMP has a well understood safety profile and is well tolerated. Data relating to serious adverse events collected within the IRONMAN trial so far indicate that 1.5% of SAEs received (prior to 28/02/18) are considered related to the administration of IMP within this patient group. As such, and taking into account the increased levels of hospitalisation for cardiovascular morbidity within IRONMAN participants, the following process will be followed for all SAEs. **9.2.1 Recording of Events of Special Interest and SAEs, by the site, via the eCRF** **All Serious Adverse Events (SAEs) occurring during the trial must be recorded within the eCRF.** Serious Adverse Events will be recorded, as appropriate, from the point of randomisation until the end of the study. In addition, all emergency day case treatments for heart failure (e.g. IV infusions of furosemide) or day	Reworking for clarification of the events that need to be recorded on the eCRF by site staff, including addition of section header. The initial protocol aimed to exclude expected cardiovascular events from reporting to sponsor. These amendments clarify that the only events to be reportable to Sponsor are those thought to be due to IMP or non-cardiovascular in nature. Given the high level of hospitalisations for cardiovascular morbidity/mortality within the patient group, and the well understood safety profile of

Protocol page	V3.0 text	V4.0 text	Reason for change
	events or hospitalisation during which a CV event occurs). A cardiovascular admission will be taken to be any admission that does not have a clear non-cardiovascular cause. • All Serious Adverse Events occurring in participants within the standard care arm as there is no IMP exposure within this participant group. All Serious Adverse Events will be subject to review by the Principal Investigator or an authorised clinician. Serious adverse events meeting the following criteria will be subject to expedited review by the PV Office following clinical review: • Any Serious Adverse Event considered related to trial treatment occurring within 30 days of treatment with the IMP; including any cardiovascular deaths or hospitalisations considered related to IMP administration. • Any Serious Adverse Event occurring within the IMP arm not considered to be a cardiovascular hospitalisation or cardiovascular death and occurring within 30 days of treatment with IMP.	case/elective admissions for percutaneous coronary intervention or cardiac device insertion should be recorded as SAEs within the eCRF. Under seriousness criteria this should be classified as a 'medically significant event'. The following should not be recorded as SAEs: • Routine treatment or monitoring of heart failure not associated with any deterioration in condition • Treatment which was elective or pre-planned, for a pre-existing non-cardiac condition not associated with any deterioration in condition e.g. pre-planned hip replacement operation which does not lead to further complications • Any admission to hospital or other institution for general care where there was no deterioration in condition. • Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission. SAEs recorded within the eCRF will be subject to a triage process prior to submission. Sites will be asked if the event is suspected to be a cardiovascular event, a non-cardiovascular event, or an event with unknown cardiovascular aetiology. Where the event is classified as a cardiovascular event sites will be asked if the event is thought be related to IMP.	the IMP by collecting only SARs and non-cardiovascular SAEs the level of pharmacovigilance carried out by the Sponsor can be reduced with no additional risk to the patients or the trial integrity. The need to assign causality and expectedness for SAEs occurring in patients on the standard care arm has also been removed. As the patient does not receive IMP then SAEs occurring in this arm are not considered reportable to sponsor. Cardiovascular events unrelated to IMP, and events occurring within the standard care arm will be recorded within the eCRF and will be assessed by the DMC.

Protocol page	V3.0 text	V4.0 text	Reason for change
	For the purposes of the PV Office the date of Sponsor awareness of an SAE will be considered the date there is any indication the event is linked to the administration of IMP. **Exclusions from SAE reporting** Hospitalisation for the following reasons will not be considered to be SAEs: • Routine treatment or monitoring of heart failure not associated with any deterioration in condition. • Treatment which was elective or pre-planned, for a pre-existing non-cardiac condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications. • Any admission to hospital or other institution for general care where there was no deterioration in condition. • Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission. For the avoidance of doubt, all emergency day case treatments for heart failure or involving percutaneous coronary intervention or cardiac	For clarification, if there is any doubt as to whether the event is cardiovascular in nature at the time the SAE is entered onto the system then the SAE should be classified as being of unknown cardiovascular aetiology. All SAEs arising during the clinical trial will be recorded in the eCRF as soon as reasonably practicable and in any event within 24 hours of first becoming aware of the event. Any change of condition or other follow-up information should be added to the eCRF as soon as it is available or at least within 24 hours of the information becoming available. Events should be followed up until the event has resolved or a final outcome has been reached, until 30 days after the end of trial. If recording in the eCRF is not possible a paper SAE form should be completed: 3. 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.	

Protocol page	V3.0 text	V4.0 text	Reason for change
	device insertion should be included. 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. AEs will be recorded from consent until the later of 30 days post cessation of trial treatment or the end of the study. All Events of Special Interest, SAEs and SUSARs will be recorded in the participant's medical records and on the eCRF, and will be recorded from the point of randomisation until the later of 30 days post cessation of trial treatment or the end of the study. Additional events identified only through record linkage will generate SAE records in the eCRF, and should be recorded in the participant's medical records in the same way as AEs. Events of Special Interest A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). B) Haemorrhage classified by site and severity • Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible)	4. 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. **9.2.2 Assessment of site reported Adverse Events** All adverse events must be assessed for seriousness. All SAEs must also be assessed for severity, causality and expectedness with reference to this protocol and the Reference Safety Information (RSI). This assessment is the responsibility of the PI or medically qualified designee and should be carried out in a timely fashion, normally within 5 days of the SAE being reported by the site. This will be facilitated by automated emails. **Assessment of seriousness** An adverse event will be considered serious if it: 1. results in death 2. is life threatening 3. requires hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability or incapacity 5. consists of a congenital anomaly or birth defect 6. is otherwise considered medically significant by the investigator **Assessment of causality** i.e. does the event have a "reasonable causal relationship" with trial medication. The following categories are used:	

Protocol page	V3.0 text	V4.0 text	Reason for change
	• Severity:- major if both acute and requiring urgent transfusion and minor if not fulfilling these criteria For each Event of Special Interest the following information will be recorded: • Nature of the event • event duration (start and end dates, if applicable) • relationship to study drug (if applicable) • outcome (if applicable) Events of Special Interest will be monitored and followed up (if applicable until the event has resolved or a final outcome has been reached). 9.3.1 Site Reported 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. The following information will be collected: • full details in medical terms and a case description • event duration (start and end dates, if applicable) • action taken • outcome • seriousness criteria • causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator • if related, whether the reaction would be considered expected or unexpected. Any change of condition or other follow-up information	None: The event is not considered to be related to the study drug. Possible: Although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible. Probable: The temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug. Definite: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause. For participants on the standard care arm, no assessment of causality is required as patients do not receive trial IMP. **Assessment of expectedness** If the event is considered to be related (possibly, probably or definitely) to the study medication, an assessment should be made of the expectedness of the reaction i.e. is the reaction a recognised adverse effect of the medication. The expectedness of an adverse reaction is assessed against the Reference Safety Information (RSI) i.e. the information regarding expected reactions detailed in Section 4.8 (Undesirable effects) of the approved Summary of Product Characteristics for Monofer® 100mg/ml solution for injection/infusion.	

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	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 All adverse events must be assessed for seriousness. All SAEs must also be assessed for severity, causality and expectedness with reference to this protocol and the Reference Safety Information (RSI). This assessment is the responsibility of the PI or medically qualified designee. Assessment of seriousness An adverse event will be considered serious if it: 1. results in death 2. is life threatening 3. requires hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability or incapacity 5. consists of a congenital anomaly or birth defect 6. is otherwise considered medically significant by the investigator Assessment of causality i.e. does the event have a "reasonable causal relationship" with trial medication. The following categories are used: None: The event is not considered to be related to the study drug. Possible: Although a relationship to the study drug cannot be completely ruled out,	Expected: consistent with the relevant product information documented in the RSI. Unexpected: not consistent with the relevant product information documented in the RSI. For participants on the standard care arm, no assessment of expectedness is required as patients do not receive trial IMP. Assessment of severity This should be assessed and described using the following categories: • Mild-awareness of event but easily tolerated • Moderate-discomfort enough to cause some interference with usual activity • Severe-inability to carry out usual activity. **9.2.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)** Any SAE assigned by the PI or delegate and by the CI (on behalf of the sponsor) or by the CI or designee in the case of events identified only by record linkage, as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as a SUSAR and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment both	

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	the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible. Probable: The temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug. Definite: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause. For participants on the standard care arm, no assessment of causality is required as patients do not receive trial IMP. Assessment of expectedness. If the event is considered to be related (possibly, probably or definitely) to the study medication, an assessment should be made of the expectedness of the reaction i.e. is the reaction a recognised adverse effect of the medication. The expectedness of an adverse reaction is assessed against the Reference Safety Information (RSI) i.e. the information regarding expected reactions detailed in Section 4.8 (Undesirable effects) of the approved Summary of Product Characteristics for Monofer® 100mg/ml solution for injection/infusion. Expected: consistent with the relevant product information documented in the RSI. Unexpected: not consistent with the relevant product information documented in the RSI. Assessment of severity	opinions will be provided on the report. 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. **9.2.4 Assessment of Record Linkage reported Serious Adverse Events** Previously unreported SAEs identified via record linkage will be reviewed and assessed for relatedness and expectedness by the Chief Investigator or his designee. The PI and/or designee will be notified when additional SAEs have been created in the system from record linkage. **9.2.5 Recording of AEs, Events of Special Interest and SAEs in patient's clinical notes** In addition to recording via the eCRF (see section 9.2.1) all AEs occurring during the trial that	

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	This should be assessed and described using the following categories: • Mild-awareness of event but easily tolerated • Moderate-discomfort enough to cause some interference with usual activity • Severe-inability to carry out usual activity. For participants on the standard care arm, no assessment of expectedness is required as patients do not receive trial IMP. 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	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. AEs will be recorded from consent. All Events of Special Interest and Serious Adverse Events will be followed up until the event has resolved or a final outcome has been reached. Additional events identified only through record linkage will auto-generate SAE records in the eCRF; however these should be recorded in the participant's medical records in the same way as AEs (see above). **9.3 Sponsor reportable SAEs (applicable to PV Office only)** Serious Adverse Events meeting the following criteria will be subject to expedited review by the Sponsor PV Office: • Any Serious Adverse Event considered related to trial treatment, including any cardiovascular deaths or hospitalisations considered related to IMP administration • Any Serious Adverse Event occurring within the IMP arm not considered to be a cardiovascular hospitalisation or cardiovascular death and occurring within 30 days of treatment with IMP The following Serious Adverse Events are efficacy outcome measures and will not be reviewed by the Sponsor PV	

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	possible with an electronic or written report. 9.3.2 Record Linkage Reported Serious Adverse Events Previously unreported SAEs identified via record linkage will be reviewed and assessed for relatedness and expectedness by the Chief Investigator or his designee. The PI and/or designee will be notified when additional SAEs have been created in the system from record linkage. 9.3.3 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 upon any indication that the event is considered related to the IMP. 9.3.4 Suspected Unexpected Serious Adverse Reactions (SUSARs) Any SAE assigned by the PI or delegate and by the CI (on behalf of the sponsor) or by the CI or designee in the case of events identified only by record linkage, as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as a SUSAR and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment both opinions will be provided on the report.	Office as they are considered expected events within this participant population: • Cardiovascular mortality unrelated to trial treatment. • Cardiovascular hospitalisation (including hospitalisations for CV events or hospitalisation during which a CV event occurs) unrelated to trial treatment. A cardiovascular admission will be taken to be any admission that does not have a clear non-cardiovascular cause. • All Serious Adverse Events occurring in participants within the standard care arm as there is no IMP exposure within this participant group. Where a Serious Adverse Event is initially not subject to sponsor review but later becomes reportable under sponsor requirements (for example, a cardiovascular hospitalisation initially reported as unrelated to IMP that upon further clinical review is considered related to treatment) the Date of Sponsor Awareness will be the date there is any indication that the event is linked to administration of IMP. **9.4 Oversight of Adverse Events** In addition to the sponsor's oversight, see section 9.3, all events recorded in the eCRF will be coded, summarised and reported to the TSC and IDMC.	

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	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.		
58	9.4 Responsibilities for Safety Reporting and Review	9.5 Responsibilities for Safety Reporting and Review	Sub-section number change due to section revision
59	9.5 Pregnancy reporting	9.6 Pregnancy reporting	Sub-section number change due to section revision
59	9.6 Overdose	9.7 Overdose	Sub-section number change due to section revision
60	9.7 Reporting urgent safety measures	9.8 Reporting urgent safety measures	Sub-section number change due to section revision
60	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.	9.9 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.	Sub-section number change due to section revision. Clarification on expected follow up of events.

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60	9.9 Development safety update reports	9.10 Development safety update reports	Sub-section number change due to section revision
76		Appendix 4 – Amendment History	Updated with details of protocol v4.0

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2 (and on footer throughout)	Version 4.0 (18/09/2019)	Version 5.0 (16/12/2020)	Updated
7	Professor John Cleland j.cleland@imperial.ac.uk Tel: 01895 453 833	Professor John Cleland John.Cleland@glasgow.ac.uk Tel: 0141 330 4744	Update to contact details
7	Professor Iain Macdougall iain.macdougall@nhs.net Tel. 020 3299 6233	Professor Iain Macdougall iain.macdougall11@gmail.com	Update to contact details
9	*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	*Treatment Duration* Average of approximately 4 years (event driven trial, expected maximum around 5.5 years, minimum around 6 months – anticipated about 5 years recruitment and a projected further minimum of 6 months of treatment/assessments, giving a range of projected patient participation of around 6 months – 5.5 years). Follow up duration Minimum of 6 months follow-up from last patient recruited, unless the study is stopped prematurely. Planned Trial Period Approximately 5.5 years	To reflect changes to the study timeline. Given that recruitment was slower than originally anticipated, and a temporary halt in recruitment from 16/03/2020 due to the Covid-19 pandemic, the recruitment period will have to be extended to allow the target of 1300 patients to be reached. In addition, the observed event rate is lower than expected, probably due to the mix of patients recruited being more biased towards stable outpatients, rather than hospitalised patients. The maximum follow-up period will therefore continue beyond the

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			original projection of 4.5 years.
10	*SECONDARY EFFICACY* 8. Days dead or hospitalised at 2.5 years (minimum duration of follow-up) 9. Quality-adjusted days alive and out of hospital at 2.5 years	*SECONDARY EFFICACY* 8. Days dead or hospitalised at 3 years 9. Quality-adjusted days alive and out of hospital at 3 years	We have extended the time line for this analysis due to the longer duration of follow-up in the study. In addition, due to the much longer period of recruitment, the reference to 'minimum duration of follow-up' is no longer relevant.
11	Investigational Medicinal Product(s) Iron isomaltoside 1000	Investigational Medicinal Product(s) Ferric derisomaltose	The UK generic name for Monofer changes in 2020 from iron isomaltoside 1000 to ferric derisomaltose to align with the international non-proprietary name (INN).
13	The TSC will meet at the start of the study, and annually thereafter.	The TSC will meet at the start of the study, and annually (or more frequently as required) thereafter.	To allow for flexibility in meeting frequency.
13	The IDMC will meet approximately every six months, with formal interim analyses when approximately 40% and 70% of the target number of adjudicated study outcomes have been observed.	The IDMC will meet approximately every six months, with formal interim analyses when approximately 50% and 70% of the target number of adjudicated study outcomes have been observed.	Due to the proposed reduction in the number of target outcomes required as a consequence of changes to the powering of the study, 40% of the revised target have already been observed. As such we feel it that it would be more appropriate for the interim analysis to be

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			carried out once 50% of the target number of end points have been observed. The IDMC are supportive of this change.
15 (v4.0)	Professor Tara Dean has extensive research expertise in large-scale study development.		Removed as Professor Dean has not been involved in the study
20	*TRIAL FLOW CHART*	*TRIAL FLOW CHART - updated*	To reflect changes noted elsewhere in protocol
21-24	*SCHEDULE OF ASSESSMENTS*	*SCHEDULE OF ASSESSMENTS* – updated	To reflect changes noted elsewhere in protocol
25	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	Visits 7 to the final patient visit will be held at 4-monthly intervals.	To reflect changes noted elsewhere in protocol.
27	It is an investigator designed and initiated study supported by the British Heart Foundation and by an additional grant from Pharmacosmos (the manufacturer of Monofer® which is approved for treating iron deficiency).	It is an investigator designed and initiated study supported by the British Heart Foundation and by an additional grant from Pharmacosmos (the manufacturer of Monofer®, ferric derisomaltose, which is approved for treating iron deficiency).	To reflect the change in the UK generic name for Monofer.
27	IRONMAN will therefore assess whether the addition of IV iron isomaltoside to guideline-indicated therapy for CHF reduces morbidity and mortality in patients with iron deficiency and is cost-effective. Iron isomaltoside is licenced for the treatment of iron deficiency.	IRONMAN will therefore assess whether the addition of IV ferric derisomaltose to guideline-indicated therapy for CHF reduces morbidity and mortality in patients with iron deficiency and is cost-effective. Ferric derisomaltose is licenced for the treatment of iron deficiency.	To reflect the change in the UK generic name for Monofer.

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28	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 [17] 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.	Newer preparations, including ferric derisomaltose, 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 [17] 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 ferric derisomaltose according to the Summary of Product Characteristics (SmPC) will not be included in the study.	To reflect the change in the UK generic name for Monofer.
29	Iron isomaltoside 1000 is approved for treatment of iron deficiency (either absolute or functional, see section 8).	Ferric derisomaltose is approved for treatment of iron deficiency (either absolute or functional, see section 8).	To reflect the change in the UK generic name for Monofer.
29	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.	Hypothesis Addition of IV ferric derisomaltose 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.	To reflect the change in the UK generic name for Monofer.
30	*SECONDARY EFFICACY*	*SECONDARY EFFICACY*	We have extended the timeline for

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	8. Days dead or hospitalised at 2.5 years (minimum duration of follow-up) 9. Quality-adjusted days alive and out of hospital at 2.5 years	8. Days dead or hospitalised at 3 years 9. Quality-adjusted days alive and out of hospital at 3 years	this analysis due to the longer duration of follow-up in the study. In addition, due to the much longer period of recruitment, the reference to 'minimum duration of follow-up' is no longer relevant.
30	3.4 Exploratory endpoints/outcomes (i) In order to understand the mechanism of any potential benefit of IV iron on the described endpoints the study will compare haemoglobin, platelets, serum creatinine and eGFR between the groups at 4 months, 20 months and at the end of the study (most recent value taken). (ii) In order to understand the impact of IV iron on iron status and its relationship to any potential benefit; assessment of serum ferritin and TSAT will be compared at 4 and 20 months between groups. This analysis will only be performed on patients entering the biobank substudy.	3.4 Exploratory endpoints/outcomes (i) In order to understand the mechanism of any potential benefit of IV iron on the described endpoints the study will compare haemoglobin, platelets, serum creatinine and eGFR between the groups at 4 months and 20 months, with all but platelets also assessed at the patient's last measurement. (ii) In order to understand the impact of IV iron on iron status and its relationship to any potential benefit; assessment of serum ferritin and TSAT will be compared at approximately 4 and 20 months between groups. This analysis will only be performed on patients entering the biobank substudy.	To clarify the measures which will be compared at the stated time points. To take account of the fact that the biobank bloods may have been taken at a later visit (due to having no face-to-face visits during the COVID-19 outbreak).
31	(iv) Extended follow-up by electronic record linkage Patient consent for national electronic record linkage in each of the participating countries will be obtained permitting assessment of events in the year prior to inclusion in the study and impact of the period of	(iv) Extended follow-up by electronic record linkage Patient consent for national electronic record linkage in each of the participating countries will be obtained permitting assessment of events in the year prior to inclusion in the study and impact of the period of	If the study is positive for the combined primary end point of cardiovascular death (CV) and heart failure hospitalisation, it will then be important to

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	randomised treatment on long-term mortality and hospital admission (analysed 2 years after study completion in the first instance).	randomised treatment on long-term mortality and hospital admission (analysed at 1 and 2 years after the last patient follow-up).	establish whether the benefit is consistent on both individual components. Whilst these are considered separately in the secondary analysis, the proposed reduction in the total number of end points required will impact on the number of CV deaths. After patients are treated with IV iron and are made iron replete, they may go many months without need for more IV iron. Analysis of events, including CV death, at 1 and 2 years post completion of the trial will permit us to assess the legacy effect of treating iron deficiency on outcomes and on mortality in particular using a larger number of events.
31	(v) 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	(v) 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. (Note that if a patient's 4 or 20	To take account of the fact that the biobank bloods may have been taken at a later visit (due to having no face-to-face visits during the COVID-19 outbreak).

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	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.	month visit has taken place remotely during the COVID-19 pandemic, the biobank bloods may be taken at the next available visit (see section 7.8.1).). 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. Additional assays may be carried out at other laboratories. Material transfer agreements will be required before the transfer of samples to other laboratories.	To clarify that some analyses may not be carried out in the laboratory at the University of Leicester.
31	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.	It is event driven and designed to assess the superiority of the addition of IV ferric derisomaltose to guideline-indicated therapy as compared with guideline-indicated therapy alone for patients with CHF and iron deficiency.	To reflect the change in the UK generic name for Monofer.
34	Participants consenting for the study will also be invited to provide optional consent for long-term follow-up (maximum 10	Participants consenting for the study will also be invited to provide optional consent for long-term follow-up (maximum 10 years) of their	To reflect that patients are also asked to consent for their medical records to be

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	years) of their electronic medical records.	electronic medical records and retrospective linkage for one year prior to consent.	checked for one year prior to the date they gave consent. (We already have approval for this and patients have consented to this – this amendment is just for clarification.)
35	7.1.4 Randomisation	7.1.5 Randomisation	Correction of typographical error
45	Bloods for storage if recruited to biomarkers sub-study Approximately 15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA. Blood will be centrifuged at 1500g for 20mins at 4oC. 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.	Bloods for storage if recruited to biomarkers sub-study Approximately 15mls of venous blood will be withdrawn and collected in pre-chilled sterilins containing EDTA. Blood will be centrifuged at 1500g for 20mins at 4oC. 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. Note that if a patient's 4 or 20 month visit has taken place remotely during the COVID-19 pandemic, the biobank bloods may be taken at the next available visit (see section 7.8.1). This will be recorded on an 'ad-hoc biobank form' on the eCRF.	To highlight that any biobank bloods missed due to a 4 month or 20 month visit being carried out remotely can be collected at the next face-to-face visit.
45	7.5.2.5 End of Study visit LPLV is expected to be approximately 4.5 years from first randomisation. <u>Medications</u> • As per baseline but excluding drugs for the	7.5.2.5 Final patient visit The CTU will monitor the accumulation of primary endpoints or other reasons for terminating the trial and will notify sites when to schedule each final patient visit. The final patient visit should take	Renaming of visit for clarification ('end of study' may be mistaken as database lock). To provide additional clarity

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	treatment of COPD/asthma and other prescribed drugs patient is regularly taking (noted in the free text box at baseline) • Patients in both arms should be asked regarding use of oral and IV iron. • Heart Failure medications. • Treatments for anaemia (including ESA) <u>Clinical and functional assessment</u> • systolic and diastolic blood pressure (after 5 minutes rest) • heart rate (after 5 minutes rest) • weight (clothed without coat and shoes) • oedema (none, minor, moderate, severe) • NYHA class (I-IV) <u>Quality of life assessments</u> • EQ-5D <u>Serious adverse events</u> <u>Events of Special Interest</u> A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). B) Haemorrhage classified by site and severity • Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible) • Severity:- major if both acute and requiring	place no later than 4.5 months after the patient's previous visit. The following data should be collected: Bloods • Bloods must be collected either during the study visit or in advance of the visit; blood results within 3 weeks of the visit taken as per standard clinical pathways can be used. Results required: • Creatinine, eGFR (MDRD/CKD-EPI) – 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 infusion visit (if necessary) to ensure that the infusion can take place as planned. To evaluate the longer term effects of the IV iron on death and hospitalisations we will be re-dosing those who meet the study criteria and data will be followed up by record linkage (at one and two years in the first instance). This will help understand the legacy from making patients iron replete. <u>Medications</u> • As per baseline but excluding drugs for the treatment of COPD/asthma and other prescribed drugs patient is regularly taking	of the data to be collected at the final patient visit. Bloods will be collected and a final infusion will be given to the IV iron arm patients if the criteria are met. This is in line with current consent. As noted on page 31 (see above), to evaluate the longer term effects of the IV iron on death and hospitalisations we will be re-dosing those who meet the study criteria and data will be followed up by record linkage (at one and two years in the first instance). This will help understand the legacy from making patients iron replete.

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	urgent transfusion and minor if not fulfilling these criteria	(noted in the free text box at baseline) • Patients in both arms should be asked regarding use of oral and IV iron. • Heart Failure medications. • Treatments for anaemia (including ESA) Clinical and functional assessment • systolic and diastolic blood pressure (after 5 minutes rest) • heart rate (after 5 minutes rest) • weight (clothed without coat and shoes) • oedema (none, minor, moderate, severe) • NYHA class (I-IV) <u>Clinical and functional assessment</u> • systolic and diastolic blood pressure (after 5 minutes rest) • heart rate (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 <u>Serious adverse events</u> • As well as any recent events, study staff will be asked to confirm that all serious adverse events occurring during the trial have been reported <u>Study Iron Infusion</u>	

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		Document dose of iron given. Events of Special Interest A) Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). B) Haemorrhage classified by site and severity • Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible) • Severity:- major if both acute and requiring urgent transfusion and minor if not fulfilling these criteria The patient should also be asked to confirm if they would like to receive a summary of the study results.	
48	Participants experiencing severe hypersensitivity to iron isomaltoside 1000 or other parenteral iron products should be withdrawn from the study treatment – see also flow chart (Appendix 2) for handling infusion reactions.	Participants experiencing severe hypersensitivity to ferric derisomaltose or other parenteral iron products should be withdrawn from the study treatment – see also flow chart (Appendix 2) for handling infusion reactions.	To reflect the change in the UK generic name for Monofer.
49	7.8.1 Sample collection and processing • Samples will be appropriately labelled in accordance with the trial procedures to comply with the 1998 Data Protection Act.	7.8.1 Sample collection and processing • Samples will be appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act and the General Data Protection Regulation.	To take into account changes that occurred with the introduction of the Data Protection Act 2018 and GDPR.
49	*7.8.1 Sample collection and processing* • Blood will be taken at baseline, 4 months and 20 months.	*7.8.1 Sample collection and processing* • Blood will be taken at baseline, 4 months and 20 months (or next available visit	To highlight that any biobank bloods missed due to a 4 month or 20 month visit being carried out

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		– due to the unprecedented impact of COVID-19 on the delivery of research in 2020 there have inevitably been challenges to see patients face-to-face. Whilst patients may have still had remote study visits, this will have impacted on patients who were due to attend and have additional samples for biobank. Sites are encouraged to take biobank samples at the next available face-to-face visit.)	remotely can be collected at the next face-to-face visit.
50	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.	7.9 End of trial As this is a morbidity/mortality endpoint driven trial, the end of the trial will be defined to be the date the study endpoints are identified, adjudicated and the database is locked. The study may be stopped prior to the target number of primary endpoints being reached 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 external factors that prevent the target number of events being reached. Once it is anticipated that the desired number of primary endpoints will be achieved or the study is to be terminated for other reasons, final study follow-up dates will be assigned to each participant. This will be done independently of randomised treatment group and of any study data.	To clarify more clearly the criteria for defining the end of the trial. Noting the impact COVID-19 has had on all research it seems sensible to give provision for the study to be stopped for other external reasons e.g. due to worsening impact of COVID-19 on the trial or withdrawal of trial funding.
50	8.1 Name and description of investigational medicinal products(s) Iron (III) isomaltoside 1000 (Monofer®) Monofer® (Iron (III) isomaltoside 1000) is an	8.1 Name and description of investigational medicinal products(s) Ferric derisomaltose (Monofer®) Monofer® (ferric derisomaltose) is an	To reflect the change in the UK generic name for Monofer.

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	intravenous (IV) iron compound manufactured by Pharmacosmos A/S (Holbaek, Denmark). Iron isomaltoside 1000 is a complex between iron and a carbohydrate moiety. The carbohydrate isomaltoside 1000 is a purely linear chemical structure as shown by 13C nuclear magnetic resonance (NMR) of repeating α-(1-6) linked glucopyranose residues. Thus, it is structurally different from the branched dextran polysaccharides present in iron dextran. Isomaltoside 1000 consists predominantly of 3-5 glucose units and is prepared from oligomers used for prevention of dextran-induced anaphylactic reaction. These oligomers have been chemically modified to further reduce the potential for anaphylactic/anaphylactoid reaction. Thus, isomaltoside 1000 is not a dextran and due to the low anaphylactic potential of isomaltoside 1000 there is no requirement for a test dose [19]. Iron isomaltoside 1000 has strongly bound iron within the iron isomaltoside formulation, which enables a controlled, slow release of bioavailable iron to the iron-binding proteins with only a low risk of free iron toxicity [19]. This allows flexible dosing, including high and rapid dosing. Following IV administration, iron isomaltoside 1000 is	intravenous (IV) iron compound manufactured by Pharmacosmos A/S (Holbaek, Denmark). Ferric derisomaltose is a complex between iron and a carbohydrate moiety. The carbohydrate moiety is a purely linear chemical structure as shown by 13C nuclear magnetic resonance (NMR) of repeating α-(1-6) linked glucopyranose residues. Thus, it is structurally different from the branched dextran polysaccharides present in iron dextran. The derisomaltose component of ferric derisomaltose consists predominantly of 3-5 glucose units and is prepared from oligomers used for prevention of dextran-induced anaphylactic reaction. These oligomers have been chemically modified to further reduce the potential for anaphylactic/anaphylactoid reaction. Thus, derisomaltose is not a dextran and due to the low anaphylactic potential of ferric derisomaltose there is no requirement for a test dose [19]. The Monofer formulation has strongly bound iron within the iron-carbohydrate complex, which enables a controlled, slow release of bioavailable iron to the iron-binding proteins with only a low risk of free iron toxicity [19]. This allows flexible dosing, including high and rapid dosing. Following IV administration, ferric derisomaltose is rapidly taken up by the cells in the reticuloendothelial system, particularly in the liver and spleen. Due to its molecular	

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	rapidly taken up by the cells in the reticuloendothelial system, particularly in the liver and spleen. Due to its molecular weight it is not eliminated by the kidneys [20]. Monofer® aqueous solution for injection/infusion contains 100mg/ml iron (as iron (III) isomaltoside 1000). Study sites will be provided with the following: • Monofer® 5 ml vials containing 500 mg iron as iron (III) isomaltoside 1000 • Monofer® 10 ml vials containing 1,000 mg iron as iron (III) isomaltoside 1000 8.2 Legal status of Monofer® Monofer® (Iron isomaltoside 1000) is currently registered in more than 20 European countries (including UK) and in a number of countries outside Europe. In Europe, iron isomaltoside 1000 is approved for treatment of iron deficiency in patients (either absolute or functional) in whom oral iron administration is unsatisfactory or impossible or where there is a clinical need to deliver iron rapidly.	weight it is not eliminated by the kidneys [20]. Monofer® aqueous solution for injection/infusion contains 100mg/ml iron (as ferric derisomaltose). Study sites will be provided with the following: • Monofer® 5 ml vials containing 500 mg iron as ferric derisomaltose • Monofer® 10 ml vials containing 1,000 mg iron as ferric derisomaltose Note: The UK generic name for Monofer changed in 2020 from iron isomaltoside 1000 to ferric derisomaltose to align with the international non-proprietary name (INN). Only the generic name was changed and there was otherwise no change to the medicine or its presentation. 8.2 Legal status of Monofer® Monofer® (ferric derisomaltose) is currently registered in more than 20 European countries (including UK) and in a number of countries outside Europe. In Europe, ferric derisomaltose is approved for treatment of iron deficiency in patients (either absolute or functional) in whom oral iron administration is unsatisfactory or impossible or where there is a clinical need to deliver iron rapidly.	
52	8.5 Preparation and administration of iron (III) isomaltoside 1000	8.5 Preparation and administration of ferric derisomaltose	To reflect the change in the UK generic name for Monofer.
53	Iron to be administered as iron (III) isomaltoside 1000.	Iron to be administered as ferric derisomaltose.	To reflect the change in the UK

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			generic name for Monofer.
53	8.8 Known drug reactions and interaction with other therapies Participants with hypersensitivity to the active substance, to iron isomaltoside 1000, or any of its excipients and/or known serious hypersensitivity to other parenteral iron products are excluded from the trial.	8.8 Known drug reactions and interaction with other therapies Participants with hypersensitivity to the active substance, to ferric derisomaltose, or any of its excipients and/or known serious hypersensitivity to other parenteral iron products are excluded from the trial.	To reflect the change in the UK generic name for Monofer.
54	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.	8.11 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. Ferric derisomaltose will be administered by health care professionals who will record the amount of drug administered to the participant in the eCRF.	To reflect the change in the UK generic name for Monofer.
55	9.2 Operational definitions for (S)AEs IRONMAN is a phase IV trial, and the iron (III) Monofer® isomaltoside as IMP has a well understood safety profile and is well tolerated. Data relating to serious adverse events collected within the IRONMAN trial so far indicate that 1.5% of SAEs received (prior to 28/02/18) are considered related to the administration of IMP within this patient group. As such, and taking into account the increased levels of hospitalisation for cardiovascular morbidity	9.2 Operational definitions for (S)AEs IRONMAN is a phase IV trial and the IMP utilised (ferric derisomaltose) has a well understood safety profile and is well tolerated. Data relating to serious adverse events collected within the IRONMAN trial to date (to (01/05/2020) indicate that less than 0.3% of SAEs received are considered related to the IMP within this patient group. In addition, participants taking part in this trial are subject to increased levels of hospitalisation due to their diagnosis heart failure. Hospitalisations within the	Very few of the SAEs received for IRONMAN to date are related to the IMP with the vast majority being related to patients' underlying cardiovascular disease. In addition patients are only treated should they meet the criteria defined in the protocol with the decision to treat being made at follow up visits that may be many months apart. As such for pharmacovigilance

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	within IRONMAN participants, the following process will be followed for all SAEs.	patient group are often for management of the underlying disease, progression of their condition, or due to management of related comorbidities. While these events are important for monitoring participant safety within the trial, they are unlikely to be related to administration of trial IMP. As such, the pharmacovigilance for this trial will be risk adapted to reflect the demonstrated low level of adverse effects of the IMP on patients.	purposes the collection of SAE data has been risk adapted to focus on the period of the participants exposure to IMP rather than those SAEs that are more likely to be due to underlying health conditions and highly unlikely to be related to IMP. SAES will be considered reportable to sponsor for participants on the IMP arm, and from the date of IMP administration plus 20 days, reflecting the time to effective elimination of circulating IMP. A secondary aim of this risk adaptation is to reduce the burden on sites and the PV office during the COVID 19 pandemic and through the remainder of the trial.
54 (v4.0)	SAEs recorded within the eCRF will be subject to a triage process prior to submission. Sites will be asked if the event is suspected to be a cardiovascular event, a non-cardiovascular event, or an event with unknown cardiovascular aetiology. Where the event is classified as a cardiovascular event sites		See above

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	will be asked if the event is thought be related to IMP. For clarification, if there is any doubt as to whether the event is cardiovascular in nature at the time the SAE is entered onto the system then the SAE should be classified as being of unknown cardiovascular aetiology.		
57	9.2.2 Assessment of site reported Adverse Events All adverse events must be assessed for seriousness. All SAEs must also be assessed for severity, causality and expectedness with reference to this protocol and the Reference Safety Information (RSI). This assessment is the responsibility of the PI or medically qualified designee and should be carried out in a timely fashion, normally within 5 days of the SAE being reported by the site. This will be facilitated by automated emails. Assessment of seriousness An adverse event will be considered serious if it: 1. results in death 2. is life threatening 3. requires hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability or incapacity 5. consists of a congenital anomaly or birth defect	9.2.2 Assessment of site reported Adverse Events All adverse events must be assessed for seriousness. All SAEs for patients on the IMP arm must also be assessed for severity, and causality with reference to this protocol and the Reference Safety Information (RSI). For patients on the standard care arm there is no requirement for the assessment of causality and expectedness. This assessment is the responsibility of the PI or their medically qualified designee and should be carried out in a timely fashion, normally within 5 days of the SAE being reported by the site. This will be facilitated by automated emails. Assessment of seriousness An adverse event will be considered serious if it: 1. results in death 2. is life threatening 3. requires hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability or incapacity	See above

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	6. is otherwise considered medically significant by the investigator Assessment of causality i.e. does the event have a "reasonable causal relationship" with trial medication. The following categories are used: None: The event is not considered to be related to the study drug. Possible: Although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible. Probable: The temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug. Definite: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause. For participants on the standard care arm, no assessment of causality is required as patients do not receive trial IMP. Assessment of expectedness If the event is considered to be related (possibly, probably or definitely) to the study medication, an assessment should be made of the expectedness of the reaction i.e. is the	5. consists of a congenital anomaly or birth defect 6. is otherwise considered medically significant by the investigator Assessment of causality (IMP arm only) i.e. does the event have a "reasonable causal relationship" with trial medication. The following categories are used: None: The event is not considered to be related to the study drug. Possible: Although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible. Probable: The temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug. Definite: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause. Assessment of expectedness (IMP arm only) If the event is considered to be related (possibly, probably or definitely) to the study medication, an assessment should be made of the expectedness of the reaction i.e. is the reaction a recognised adverse effect of the medication. The expectedness of an adverse reaction is assessed against the Reference Safety	

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	reaction a recognised adverse effect of the medication. The expectedness of an adverse reaction is assessed against the Reference Safety Information (RSI) i.e. the information regarding expected reactions detailed in Section 4.8 (Undesirable effects) of the approved Summary of Product Characteristics for Monofer® 100mg/ml solution for injection/infusion. Expected: consistent with the relevant product information documented in the RSI. Unexpected: not consistent with the relevant product information documented in the RSI. For participants on the standard care arm, no assessment of expectedness is required as patients do not receive trial IMP. Assessment of severity This should be assessed and described using the following categories: • Mild-awareness of event but easily tolerated • Moderate-discomfort enough to cause some interference with usual activity • Severe-inability to carry out usual activity.	Information (RSI) i.e. the information regarding expected reactions detailed in Section 4.8 (Undesirable effects) of the approved Summary of Product Characteristics for Monofer® 100mg/ml solution for injection/infusion. Expected: consistent with the relevant product information documented in the RSI. Unexpected: not consistent with the relevant product information documented in the RSI. Assessment of severity This should be assessed and described using the following categories: • Mild-awareness of event but easily tolerated • Moderate-discomfort enough to cause some interference with usual activity • Severe-inability to carry out usual activity.	
56 (v4.0)	9.2.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)		See above

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	Any SAE assigned by the PI or delegate and by the CI (on behalf of the sponsor) or by the CI or designee in the case of events identified only by record linkage, as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as a SUSAR and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment both opinions will be provided on the report. 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		

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	accompanying CTIMP Safety Report Form.		
58	9.2.4 Assessment of Record Linkage reported Serious Adverse Events	9.2.3 Assessment of Record Linkage reported Serious Adverse Events	Sub-section number changed due to section revision
58	9.2.5 Recording of AEs, Events of Special Interest and SAEs in patient's clinical notes	9.2.4 Recording of AEs, Events of Special Interest and SAEs in patient's clinical notes	Sub-section number changed due to section revision
59	9.3 Sponsor reportable SAEs (applicable to PV Office only) Serious Adverse Events meeting the following criteria will be subject to expedited review by the Sponsor PV Office: • Any Serious Adverse Event considered related to trial treatment, including any cardiovascular deaths or hospitalisations considered related to IMP administration • Any Serious Adverse Event occurring within the IMP arm not considered to be a cardiovascular hospitalisation or cardiovascular death and occurring within 30 days of treatment with IMP The following Serious Adverse Events are efficacy outcome measures and will not be reviewed by the Sponsor PV Office as they are considered expected events within this participant population: • Cardiovascular mortality unrelated to trial treatment. • Cardiovascular hospitalisation (including	9.3 Expedited Reporting of SAEs to Sponsor PV Office and Regulatory Authorities 9.3.1 SAEs subject to expedited reporting (applicable to PV Office only) All Serious Adverse Events meeting the following criteria will be subject to expedited reporting and review by the Sponsor PV Office: • Any Serious Adverse Event judged by the reporting investigator to have a reasonable possibility of a causal relationship with the IMP irrespective of the period of time between the administration of IMP and the onset of the event • Any Serious Adverse Event occurring within the IMP arm within 20 days of treatment with IMP SAEs meeting the above criteria should be recorded within the eCRF as per section 9.2.1 and assessed by local investigators as per section 9.2.2. These SAEs will be subject to review by the Sponsor PV office. Any SAEs confirmed as SARs following review by the local investigators(s) will be assessed by the CI and/or Sponsor against the currently	See above

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	hospitalisations for CV events or hospitalisation during which a CV event occurs) unrelated to trial treatment. A cardiovascular admission will be taken to be any admission that does not have a clear non-cardiovascular cause. • All Serious Adverse Events occurring in participants within the standard care arm as there is no IMP exposure within this participant group. Where a Serious Adverse Event is initially not subject to sponsor review but later becomes reportable under sponsor requirements (for example, a cardiovascular hospitalisation initially reported as unrelated to IMP that upon further clinical review is considered related to treatment) the Date of Sponsor Awareness will be the date there is any indication that the event is linked to administration of IMP. 9.4 Oversight of Adverse Events In addition to the sponsor's oversight, see section 9.3, all events recorded in the eCRF will be coded, summarised and reported to the TSC and IDMC.	approved RSI to determine the expectedness of the event. 9.3.2 SAEs that are study outcomes and excluded from expedited reporting to the Sponsor and Regulatory Authorities For the purpose of this trial, the following SAEs will be recorded on the eCRF as study outcome events only and considered exempt from expedited reporting but are to be reported within 24 hours of site awareness as per section 9.2.1. • All Serious Adverse Events within the standard care arm as there is no IMP exposure within this participant group. • Primary efficacy outcomes o Cardiovascular mortality occurring more than 20 days following IMP o Hospitalisation for worsening heart failure (both initial and recurrent) occurring more than 20 days following IMP • Secondary and tertiary efficacy outcomes o All-cause mortality (including non-cardiovascular death and death due to undetermined cause) occurring more than 20 days following IMP o Hospitalisation for major cardiovascular events occurring more than 20 days following IMP o Hospitalisation for non-cardiovascular events	

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		occurring more than 20 days following IMP • Safety outcomes o Hospitalisation for infection occurring more than 20 days following IMP o Mortality due to infection occurring more than 20 days following IMP In addition, all Serious Adverse Events within the standard care arm are not subject to expedited reporting to the Sponsor and Regulatory Authorities as there is no IMP exposure within this participant group. <u>Oversight of events excluded from expedited reporting</u> SAEs not subject to expedited reporting will be coded and summarised. These events are subject to statistical monitoring and review by the independent data monitoring committee and trial steering committees assigned to the trial. Where potential trends are identified by the IDMC, TSC or statistical monitoring further events may be considered subject to expedited reporting to the Sponsor and Regulatory authorities. Where a Serious Adverse Event is initially not subject to sponsor review but later becomes reportable under sponsor requirements (for example, a cardiovascular hospitalisation initially reported as unrelated to IMP that upon further clinical review is considered related to treatment) the Date of	

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		Sponsor Awareness will be the date there is any indication that the event is linked to administration of IMP. 9.3.3 Suspected Unexpected Serious Adverse Reactions (SUSARs) Any SAE assigned by the PI or delegate and by the CI (on behalf of the sponsor)/Sponsor or by the CI or designee in the case of events identified only by record linkage, as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as a SUSAR and subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment both opinions will be provided on the report. 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	

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		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.	
61	9.5 Responsibilities for Safety Reporting and Review	9.4 Responsibilities for Safety Reporting and Review	Sub-section number changed due to section revision
61	Sponsor: 1. Central data collection and verification of AEs, SAEs, SARs and SUSARs according to the trial protocol 2. Reporting safety information to the CI or delegate for the ongoing assessment of the risk / benefit 3. Reporting safety information to the independent oversight committees identified for the trial (Independent Data Monitoring Committee (IDMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan. 4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines. 5. Notifying Investigators of SUSARs that occur within the trial. 6. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial. 7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely	Sponsor: 1. Central data collection and verification of AEs, SAEs, SARs and SUSARs according to the trial protocol 2. Reporting safety information to the CI or delegate for the ongoing assessment of the risk / benefit 3. Assessment and confirmation of expectedness for all reported SARs 4. Reporting safety information to the independent oversight committees identified for the trial (Independent Data Monitoring Committee (IDMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan. 5. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines. 6. Notifying Investigators of SUSARs that occur within the trial. 7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial. 8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.	See above

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	submission to the MHRA and REC.		
62	9.6 Pregnancy reporting	9.5 Pregnancy reporting	Sub-section number changed due to section revision
63	9.7 Overdose The iron(III) isomaltoside 1000 in Monofer® has a low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing.	9.6 Overdose The ferric derisomaltose in Monofer® has a low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing.	Sub-section number changed due to section revision. To reflect the change in the UK generic name for Monofer.
63	9.8 Reporting urgent safety measures	9.7 Reporting urgent safety measures	Sub-section number changed due to section revision
63	9.9 The type and duration of the follow-up of participants after adverse events	9.8 The type and duration of the follow-up of participants after adverse events	Sub-section number changed due to section revision
63	9.10 Development safety update reports	9.9 Development safety update reports	Sub-section number changed due to section revision
63	10.1 Sample size 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 [21]. 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	10.1 Sample size calculation The original anticipated primary endpoint rate in the control group was 30% in the first year and 60% by three years (median follow-up). Sample size calculations based on recurrent event analyses are complex [21]. Therefore, conservatively, we have based them on a time to first event analysis using the Wald statistic in a Cox proportional hazards model. We estimated that 570 patients per group (yielding 631 first events) would provide 80% power to detect a hazard ratio of 0.8 (20% reduction in hazard which we believed was a clinically meaningful effect). All analyses will be conducted on an intention to treat basis. We anticipate an incomplete	Recruitment to IRONMAN has been slower than expected, and this has been exacerbated by the COVID-19 pandemic during 2020. In addition, event rates have been lower than expected, meaning that the original target number of endpoints would likely not be reached until at least late 2023. The possible need to reconsent many patients for longer follow-up and the difficulty in recruiting more

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	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.	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 intended to recruit 650 patients per group. In practice, recruitment to IRONMAN has been slower than expected, an issue exacerbated by the COVID-19 pandemic, In addition, event rates have been lower than expected, meaning that the original target number of endpoints would likely not be reached until at least late 2023. The possible need to reconsent patients for longer follow-up and the difficulty in recruiting more patients and retaining existing patients made the target of 631 events unfeasible. Hence, consideration was given to modifying the study objectives. Since the start of the trial, a meta-analysis of smaller trials of IV iron in heart failure outpatients has suggested a larger treatment effect might be possible (95% CI for the rate ratio in favour of IV iron treatment 0.53 (0.33, 0.86)). Recently, the publication of the AFFIRM-AHF trial that recruited patients after an acute heart failure admission provided, in an analysis adjusting for the COVID-19 pandemic period, a rate ratio (95%CI) in favour of IV iron treatment of 0·75 (0·59, 0·96). On the basis of this information, the target number of events was recalculated based on a hazard ratio of 0.75, resulting in a new target of 379 events.	patients and retaining existing patients make the target of 631 events unfeasible. Hence, consideration was given to modifying the study objectives. Since the start of the trial, a meta-analysis of smaller trials of IV iron in heart failure outpatients has suggested a larger treatment effect might be possible (95% CI for the rate ratio in favour of IV iron treatment 0.53 (0.33, 0.86)). Recently, the publication of the AFFIRM-AHF trial that recruited patients after an acute heart failure admission provided, in an analysis adjusting for the COVID-19 pandemic period, a rate ratio (95%CI) in favour of IV iron treatment of 0·75 (0·59, 0·96). On the basis of this information, the target number of events was recalculated based on a hazard ratio of 0.75, resulting in a new target of 379 events. We feel as though this is a realistic

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			target and we hope to achieve this in around 1 year.
64	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 There are no large trials currently recruiting patients with LVEF<45% or evaluating IV iron on morbidity and mortality in heart failure. We expect that participants will be recruited over two years with a ramp-up in recruitment of the first 6 months and uniformly thereafter.	10.2 Anticipated recruitment rate We intend to recruit from up to 100 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 There are no large trials currently recruiting patients with LVEF<45% or evaluating IV iron on morbidity and mortality in heart failure in the UK. Recruitment will be over a period of around five years.	For consistency with other sections of the protocol, and to reflect the fact that the recruitment period will be longer than originally anticipated.
64	10.3 Statistical analysis 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	10.3 Statistical analysis 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 outcome will be analysed using the	To update on plans for analyses. Recent studies have shown that there is little difference in results for different methods of analysis for recurrent events.

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	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	method of Lin, Wei, Yang & Ying [22] and the data displayed graphically using the method of Ghosh & Lin [23]. In addition, this outcome will be analysed in sensitivity analyses using a joint frailty model for mortality and hospitalisations for worsening heart failure [24] to permit the estimation of the separate effects of treatment on death and heart failure hospitalisation as a recurrent event and also using the Method of Mao and Lin [25]. 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	The method of Lin, Wei, Yang and Ying is the most commonly used method. Additional methods will be explored as sensitivity analysis.

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	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.	adjusting for potential length of follow-up. Serious adverse events will be tabulated by system organ class and preferred term. In the analysis, cardiovascular death will be defined as deaths adjudicated by the endpoint committee as cardiovascular death or as death of undetermined cause. Because of the potential impact of the COVID 19 pandemic on the study results, a sensitivity analysis will be conducted excluding events occurring during the main period of the pandemic. Full analysis details will be documented in a formal statistical analysis plan that will be completed and signed off before database lock.	
65	Categorical variables: - Sex, recruitment in versus out of hospital, patients taking/not taking hypoglycaemic therapy, TSAT <20% versus ferritin <100ug/L with TSAT ≥20%.	Categorical variables: - Sex, recruitment in versus out of hospital, patients taking/not taking hypoglycaemic therapy, TSAT <20% versus ferritin <100ug/L with TSAT ≥20%, aetiology of heart failure.	Sub-group analysis from a recently published study (AFFIRM-AHF) has raised the question that aetiology of heart failure (ischaemic vs non-ischaemic) might influence response to IV iron. This will permit us to investigate this further.
65	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.	The IDMC will meet approximately every six months, with formal interim analyses for evidence of efficacy when ~50% and ~70% of the target number of primary endpoints have been adjudicated.	Due to the proposed reduction in the number of target outcomes required as a consequence of changes to the powering of the study, 40% of the revised target have already been

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			observed. As such we feel it that it would be more appropriate for the interim analysis to be carried out once 50% of end points have been observed. The IDMC are supportive of this change.
68	12 MONITORING, AUDIT & INSPECTION Monitoring will be conducted by NHS Greater Glasgow and Clyde (GG&C) 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 NHS GG&C Research Governance Manager.	12 MONITORING, AUDIT & INSPECTION Monitoring will be conducted by NHS Greater Glasgow and Clyde (GG&C) 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 NHS GG&C Research Governance Manager or Lead Clinical Trial Monitor.	To note that the Lead Clinical Trial Monitor may sign off the Monitoring Plan.
70	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.	13.7 Data protection and patient confidentiality All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 and the General Data Protection Regulation with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.	To take into account changes that occurred with the introduction of the Data Protection Act 2018 and GDPR.
73	*References*	*References – updated*	Updated to include references for additions to section 10.3
75	*Appendix 1 – Risk* IMP/Intervention	*Appendix 1 – Risk* IMP/Intervention	To reflect the change in the UK

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	IV administration of Iron-maltoside-1000	IV administration of ferric derisomaltose	generic name for Monofer.
80	*Appendix 4 – Amendment History*	*Appendix 4 – Amendment History* – updated	Updated with details of protocol v5.0

IRONMAN Protocol v6.0 summary of changes

15/12/2021

Protocol page	V5.0 text	V6.0 text	Reason for change
2 (and on footer throughout)	Version 5.0 (16/12/2020)	Version 6.0 (15/12/2021)	Updated version details
4	I also confirm that I will make the findings of the study publically available	I also confirm that I will make the findings of the study publicly available	Spelling correction
6 & 7	Dr Paul Kalra (Co CI)	Professor Paul Kalra (CI)	Update to title and correction
6	Dr Maureen Travers Tel: 0141 314 4012 E-mail: Maureen.travers@ggc.scot.nhs.uk	Dr Pamela Sandu Tel: 0141 314 4414 E-mail: pamela.sandu@ggc.scot.nhs.uk	Change of NHS Greater Glasgow and Clyde sponsor coordinator.
9	Planned Sample Size - 1300	Planned Sample Size - 1160	The COVID 19 pandemic has had a major impact on the ability of study sites to recruit new patients. As the study is event driven, we believe that the most efficient approach to enable successful completion of the study is to slightly extend patient follow-up rather than to struggle to complete the original sample size target of 1300. We believe that 1160 is an achievable target.
9	Treatment Duration	Treatment Duration	IRONMAN is an event driven

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	Average of approximately 4 years (event driven trial, expected maximum around 5.5 years, minimum around 6 months – anticipated about 5 years recruitment and a projected further minimum of 6 months of treatment/assessments, giving a range of projected patient participation of around 6 months – 5.5 years). Follow up duration Minimum of 6 months follow-up from last patient recruited, unless the study is stopped prematurely.	Average of approximately 4 years (event driven trial, expected maximum around 5.5 years, minimum around 3 months – anticipated about 5 years recruitment and a projected further minimum of 3 months of treatment/assessments, giving a range of projected patient participation of around 3 months – 5.5 years). Follow up duration Minimum of 3 months follow-up from last patient recruited, unless the study is stopped prematurely.	study with a target of 379 first primary endpoints. We now project that we will reach this target very early in 2022. As we have just stopped recruitment and final visits will take place in January to mid-March 2022, some patients may only have 3 months follow-up, hence this change to the protocol. As very few patients have been recruited in the past three months, this change will impact very few patients.
15	Dr Paul Kalra	Professor Paul Kalra	Update to title
20	*TRIAL FLOW CHART*	*TRIAL FLOW CHART - updated*	Update to drug name (missed in previous version of protocol) and number of patients
21	Final patient visit To be completed at participant's scheduled Final patient visit. Visit window to be notified by the CTU. LPLV is expected to be approximately 5 years from first randomisation.	Final patient visit To be completed at participant's scheduled Final patient visit. Visit window to be notified by the CTU. LPLV is expected to be approximately 5.5 years from first randomisation.	Update to reflect timeline changes elsewhere in protocol.
47		7.6 COVID-19 COVID-19 Vaccination	Addition of section on timing of

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		For patients in the IV iron arm of the study, it is recommended that they do not receive the COVID-19 vaccine and their infusion on the same day and if possible, maintain a 7-day interval between the vaccine and infusion in order to avoid incorrect attribution of potential adverse events. Recording of COVID-19 vaccinations Participants should be asked if they have had a COVID-19 vaccine and if they have, the following information should be recorded in the medical notes: how many doses; the name of the vaccine; and approximately when they were given. COVID-19 vaccinations are not recorded on the eCRF, unless they are thought to be related to a serious adverse event, in which case they should be noted in the concomitant medications section of the SAE report.	COVID-19 vaccination in relation to IV iron infusions, and expectations for recording vaccination details. Note that the recommended 7-day interval between the vaccine and infusion is to make it easier to identify which medicines may be contributing to any adverse effects. Pharmacosmos, the manufacturer of Monofer, have not informed the sponsor to date of any safety issues/potential interactions with the deployed COVID-19 vaccines. No change has been made to the Summary of Product Characteristics and the SmPC does not list any precautions around vaccination.

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47	7.6 Retention and strategies for maximizing follow-up	7.7 Retention and strategies for maximizing follow-up	Renumbering of section
48		Where follow-up visits are being conducted remotely, sites will be permitted to post the quality of life questionnaires (EQ-5D and Minnesota Living With Heart Failure) to patients for completion. These questionnaires can also be conducted via telephone.	Some patients may still be reluctant to attend in-person visits. Allowing questionnaires to be done via telephone or posted to participants for completion at home means less missing data.
48	7.7 Treatment Interruptions and Withdrawal criteria	7.8 Treatment Interruptions and Withdrawal criteria	Renumbering of section
49	7.8 Storage and analysis of samples	7.9 Storage and analysis of samples	Renumbering of section
49	7.8.1 Sample collection and processing	7.9.1 Sample collection and processing	Renumbering of section
50	7.8.2 Sample transport to central laboratory and analysis	7.9.2 Sample transport to central laboratory and analysis	Renumbering of section
50	7.9 End of trial	7.10 End of trial	Renumbering of section
54	9.1 Definitions Adverse Event (AE) Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.	9.1 Definitions Adverse Event (AE) Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences that are not necessarily caused by or related to that product.	Grammatical amendment
55	Adverse Reaction (AR) An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.	Adverse Reaction (AR) An untoward and unintended response in a participant to an investigational medicinal product that is related to any dose administered to that participant.	Grammatical amendment
56	*Note: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.	*Note: “Severe” is used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is	Minor amendment to text

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		the regulatory definition supplied above.	
56	9.2 Operational definitions for (S)AEs IRONMAN is a phase IV trial and the IMP utilised (ferric derisomaltose) has a well understood safety profile and is well tolerated. Data relating to serious adverse events collected within the IRONMAN trial to date (to (01/05/2020) indicate that less than 0.3% of SAEs received are considered related to the IMP within this patient group. In addition, participants taking part in this trial are subject to increased levels of hospitalisation due to their diagnosis heart failure. Hospitalisations within the patient group are often for management of the underlying disease, progression of their condition, or due to management of related comorbidities. While these events are important for monitoring participant safety within the trial, they are unlikely to be related to administration of trial IMP. As such, the pharmacovigilance for this trial will be risk adapted to reflect the demonstrated low level of adverse effects of the IMP on patients.	9.2 Operational definitions for (S)AEs IRONMAN is a phase IV trial and the IMP utilised, ferric derisomaltose, has a well understood safety profile and is well tolerated. Data relating to serious adverse events collected within the IRONMAN trial to date (to 28/02/21) indicate that less than 0.13% of SAEs received are considered related to IMP within this patient group. In addition, participants taking part in this trial are subject to increased levels of hospitalisation due to their diagnosis heart failure. Hospitalisations within the patient group are often for management of the underlying disease, progression of their condition, or due to management of related comorbidities. While these events are important for monitoring participant safety within the trial, they are unlikely to be related to administration of ferric derisomaltose and are considered anticipated complications. As such, the pharmacovigilance for this trial will be risk adapted to reflect the demonstrated low level of adverse effects of the IMP on patients. The COVID-19 pandemic has led to the redeployment of some research staff to aid in the management of COVID-19 and urgent public health	Updated to reflect the current SAR rate. Addition of text to explain risk adaptation of SAE collection in response to the continued COVID19 epidemic. Principle aim is to reduce burden on sites.

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		research. It is therefore vital to minimise the burden of work on local investigators. To ensure that trial sites can focus on the key events and respond to queries from the Sponsor and data management we have simplified the SAE data collection as detailed below.	
56	9.2.1 Recording of Events of Special Interest and SAEs, by the site, via the eCRF All Serious Adverse Events (SAEs) occurring during the trial must be recorded within the eCRF. Serious Adverse Events will be recorded, as appropriate, from the point of randomisation until the end of the study. In addition, all emergency day case treatments for heart failure (e.g. IV infusions of furosemide) or day case/elective admissions for percutaneous coronary intervention or cardiac device insertion should be recorded as SAEs within the eCRF. Under seriousness criteria this should be classified as a 'medically significant event'. The following should not be recorded as SAEs: • Routine treatment or monitoring of heart failure not associated with any deterioration in condition • Treatment which was elective or pre-planned, for a pre-existing non-cardiac condition not associated with any deterioration in condition e.g. pre-planned hip replacement operation which	9.3 Recording of AEs, Events of Special Interest and SAEs in patient's clinical notes 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 attributed to trial medication or not, and should be assessed for seriousness, severity and include the start and stop dates of the event. AEs will be recorded from the date of consent until the end of their trial participation. Events of special interest as defined below should be recorded within the relevant section of the eCRF; these events are: • Blood transfusions, including reasons: trauma, surgery, haemorrhage and anaemia (this could include anaemia due to prolonged or repetitive minor blood loss). • Haemorrhage classified by site and severity o Site:- upper GI, lower GI, genitourinary (GU), Other (note – bleeding from more than one site is possible) o Severity:- major if both acute and requiring	Rewording of the section to make the SAE data collection process clearer and to clarify events that are reportable to the Sponsor and subject to expedited reporting.

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	does not lead to further complications • Any admission to hospital or other institution for general care where there was no deterioration in condition. • Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission. All SAEs arising during the clinical trial will be recorded in the eCRF as soon as reasonably practicable and in any event within 24 hours of first becoming aware of the event. Any change of condition or other follow-up information should be added to the eCRF as soon as it is available or at least within 24 hours of the information becoming available. Events should be followed up until the event has resolved or a final outcome has been reached, until 30 days after the end of trial. 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.	urgent transfusion and minor if not fulfilling these criteria Additional events identified only through record linkage will auto-generate SAE records in the eCRF; however, these should be recorded in the participant's medical records in the same way as AEs. 9.4 Recording of Serious Adverse Events All Events meeting the criteria of a serious adverse event must be recorded within the eCRF. The eCRF reporting system will triage SAEs into the relevant category at the time the event is entered onto the system. All recorded events should be assessed as follows: Assessment of seriousness An adverse event is considered serious if it: 1. results in death 2. is life threatening 3. requires hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability or incapacity 5. consists of a congenital anomaly or birth defect 6. is otherwise considered medically significant by the investigator Assessment of severity	

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	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. 9.2.2 Assessment of site reported Adverse Events All adverse events must be assessed for seriousness. All SAEs for patients on the IMP arm must also be assessed for severity, and causality with reference to this protocol and the Reference Safety Information (RSI). For patients on the standard care arm there is no requirement for the assessment of causality and expectedness. This assessment is the responsibility of the PI or their medically qualified designee and should be carried out in a timely fashion, normally within 5 days of the SAE being reported by the site. This will be facilitated by automated emails. Assessment of seriousness An adverse event will be considered serious if it: 1. results in death 2. is life threatening 3. requires hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability or incapacity 5. consists of a congenital anomaly or birth defect 6. is otherwise considered medically significant by the investigator Assessment of causality (IMP arm only) i.e. does the event have a "reasonable causal	This should be assessed and described using the following categories: • Mild: awareness of event but easily tolerated • Moderate: discomfort enough to cause some interference with usual activity • Severe: inability to carry out usual activity. The outcome for each event will also be collected and events must be followed up until a resolution is reached. The timeline for SAE reporting and how these events are assessed is dependent on whether the event is collected for determining study outcomes or for the purposes of pharmacovigilance. 9.4.1 Serious Adverse Events that are Study Outcomes only While all SAEs are to be recorded within the SAE section of the eCRF, many hospitalisations and deaths reported will be related to the participants underlying cardiovascular disease. These events are important for the analysis of the study endpoints and the monitoring differences in cardiovascular events between arms, but are not considered relevant for the purposes of pharmacovigilance due to their anticipated nature and unlikely relationship to the use of the IMP.	

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	relationship" with trial medication. The following categories are used: None: The event is not considered to be related to the study drug. Possible: Although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible. Probable: The temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug. Definite: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause. Assessment of expectedness (IMP arm only) If the event is considered to be related (possibly, probably or definitely) to the study medication, an assessment should be made of the expectedness of the reaction i.e. is the reaction a recognised adverse effect of the medication. The expectedness of an adverse reaction is assessed against the Reference Safety Information (RSI) i.e. the information regarding expected reactions detailed in Section 4.8 (Undesirable effects) of the approved Summary of Product Characteristics for Monofer® 100mg/ml solution for injection/infusion. Expected: consistent with the relevant product	As such, SAEs that occur within participants on the standard care arm and SAEs that occur more than 20 days following administration of IMP for patients on the ferric derisomaltose arm are not subject to expedited review. These events are primarily anticipated events related to the underlying medical condition of the trial participants and will be assessed as potential endpoints by the Endpoint Committee. Examples of these events are as follows: • Primary efficacy outcomes o Cardiovascular mortality occurring more than 20 days following IMP o Hospitalisation for worsening heart failure (both initial and recurrent) occurring more than 20 days following IMP • Secondary and tertiary efficacy outcomes o All-cause mortality (including non-cardiovascular death and death due to undetermined cause) occurring more than 20 days following IMP o Hospitalisation for major cardiovascular events occurring more than 20 days following IMP o Hospitalisation for non-cardiovascular events occurring more than 20 days following IMP • Safety outcomes	

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	information documented in the RSI. Unexpected: not consistent with the relevant product information documented in the RSI. Assessment of severity This should be assessed and described using the following categories: • Mild-awareness of event but easily tolerated • Moderate-discomfort enough to cause some interference with usual activity • Severe-inability to carry out usual activity. 9.2.3 Assessment of Record Linkage reported Serious Adverse Events Previously unreported SAEs identified via record linkage will be reviewed and assessed for relatedness and expectedness by the Chief Investigator or his designee. The PI and/or designee will be notified when additional SAEs have been created in the system from record linkage. 9.2.4 Recording of AEs, Events of Special Interest and SAEs in patient's clinical notes In addition to recording via the eCRF (see section 9.2.1) 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. AEs will be recorded from consent.	o Hospitalisation for infection occurring more than 20 days following IMP o Mortality due to infection occurring more than 20 days following IMP In addition to the standard definition of an SAE, all emergency day case treatments for heart failure (e.g. IV infusions of furosemide) or day case/elective admissions for percutaneous coronary intervention or cardiac device insertion should be recorded as SAEs within the eCRF. Under seriousness criteria this should be classified as a 'medically significant event'. These events must be reviewed by the local investigator and assessed for accuracy and completeness but do not require an assessment of causality and expectedness as they are not considered subject to expedited reporting and review to the Sponsor and REC. Any change of condition or other follow-up information should be added to the eCRF as soon as it is available 9.4.2 Serious Adverse Events subject to expedited reporting and review These events are collected for the purposes of monitoring IMP safety; as such they are subject to expedited reporting to the Sponsor and where applicable the MHRA and REC. These events must be reported on the eCRF within 24 hours of local	

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	All Events of Special Interest and Serious Adverse Events will be followed up until the event has resolved or a final outcome has been reached. Additional events identified only through record linkage will auto-generate SAE records in the eCRF; however these should be recorded in the participant's medical records in the same way as AEs (see above). 9.3 Expedited Reporting of SAEs to Sponsor PV Office and Regulatory Authorities 9.3.1 SAEs subject to expedited reporting (applicable to PV Office only) All Serious Adverse Events meeting the following criteria will be subject to expedited reporting and review by the Sponsor PV Office: • Any Serious Adverse Event judged by the reporting investigator to have a reasonable possibility of a causal relationship with the IMP irrespective of the period of time between the administration of IMP and the onset of the event • Any Serious Adverse Event occurring within the IMP arm within 20 days of treatment with IMP SAEs meeting the above criteria should be recorded within the eCRF as per section 9.2.1 and assessed by local investigators as per section 9.2.2. These SAEs will be subject to review by the Sponsor PV office. Any SAEs	investigators becoming aware of the event. Reportable events are as follows: • Any Serious Adverse Event judged by the reporting investigator to have a reasonable possibility of a causal relationship with the IMP irrespective of the period between the administration of IMP and the onset of the event, • Any Serious Adverse Event occurring within the IMP arm within 20 days of treatment with IMP 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, 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 07989 470505. This must be followed up as soon as possible with an electronic or written report In addition to the assessments detailed in	

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	confirmed as SARs following review by the local investigators(s) will be assessed by the CI and/or Sponsor against the currently approved RSI to determine the expectedness of the event. 9.3.2 SAEs that are study outcomes and excluded from expedited reporting to the Sponsor and Regulatory Authorities For the purpose of this trial, the following SAEs will be recorded on the eCRF as study outcome events only and considered exempt from expedited reporting but are to be reported within 24 hours of site awareness as per section 9.2.1. • All Serious Adverse Events within the standard care arm as there is no IMP exposure within this participant group. • Primary efficacy outcomes o Cardiovascular mortality occurring more than 20 days following IMP o Hospitalisation for worsening heart failure (both initial and recurrent) occurring more than 20 days following IMP • Secondary and tertiary efficacy outcomes o All-cause mortality (including non-cardiovascular death and death due to undetermined cause) occurring more than 20 days following IMP o Hospitalisation for major cardiovascular events occurring more than 20 days following IMP o Hospitalisation for non-cardiovascular events occurring more than 20 days following IMP	section 9.4 these events should also be assessed for causality and expectedness by the local investigator as detailed below: Assessment of causality i.e. does the event have a "reasonable causal relationship" with trial medication. The following categories are used: • None: The event is not considered related to the study drug. • Possible: Although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible. • Probable: The temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug. • Definite: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that the study drug is the most likely cause. Assessment of expectedness If the event is considered to be related (possibly, probably or definitely) to the study medication, an assessment should be made of the expectedness of the reaction i.e. is the reaction a recognised adverse effect of the medication. The expectedness of an adverse reaction is assessed against the Reference Safety Information (RSI) i.e. the information regarding	

Protocol page	V5.0 text	V6.0 text	Reason for change
	• Safety outcomes o Hospitalisation for infection occurring more than 20 days following IMP o Mortality due to infection occurring more than 20 days following IMP In addition, all Serious Adverse Events within the standard care arm are not subject to expedited reporting to the Sponsor and Regulatory Authorities as there is no IMP exposure within this participant group. Oversight of events excluded from expedited reporting SAEs not subject to expedited reporting will be coded and summarised. These events are subject to statistical monitoring and review by the independent data monitoring committee and trial steering committees assigned to the trial. Where potential trends are identified by the IDMC, TSC or statistical monitoring further events may be considered subject to expedited reporting to the Sponsor and Regulatory authorities. Where a Serious Adverse Event is initially not subject to sponsor review but later becomes reportable under sponsor requirements (for example, a cardiovascular hospitalisation initially reported as unrelated to IMP that upon further clinical review is considered related to treatment), the Date of Sponsor Awareness will be the date there is any indication that the event is linked to administration of IMP.	expected reactions detailed in Section 4.8 (Undesirable effects) of the approved Summary of Product Characteristics for Monofer® 100mg/ml solution for injection/infusion. • Expected: consistent with the relevant product information documented in the RSI. • Unexpected: not consistent with the relevant product information documented in the RSI. Any event assessed by the local investigators(s) as related to IMP will be assessed for expectedness by the CI/Sponsor against the currently approved RSI. Should a related event be considered unexpected it will be subject to expedited reporting to the MHRA and REC as per section 9.5. Any change of condition or other follow-up information should be added to the eCRF or 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 an outcome has been reached. COVID-19 vaccination and reporting Where a deployed COVID-19 vaccine is suspected to be involved in the onset of a reported event it should be recorded as a concomitant medication. A causal relationship between the	

Protocol page	V5.0 text	V6.0 text	Reason for change
	9.3.3 Suspected Unexpected Serious Adverse Reactions (SUSARs) Any SAE assigned by the PI or delegate and by the CI (on behalf of the sponsor) or by the CI or designee in the case of events identified only by record linkage, as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as a SUSAR and subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment both opinions will be provided on the report. 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	vaccine and the event, including potential drug interactions should be assigned by the reporting investigator. If a reported event is suspected to be due to a deployed COVID-19 vaccine alone reporting investigators should ensure that standard Yellow Card reporting procedures are followed. 9.4.3 Exclusions from the SAE recording and reporting process The events detailed below do not require reporting as SAEs: • Routine treatment or monitoring of heart failure not associated with any deterioration in condition • Treatment which was elective or pre-planned, for a pre-existing non-cardiac condition not associated with any deterioration in condition e.g. pre-planned hip replacement operation which does not lead to further complications • Any admission to hospital or other institution for general care where there was no deterioration in condition. • Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission. 9.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)	

Protocol page	V5.0 text	V6.0 text	Reason for change
	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) 1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit. 2. Using medical judgement, confirm seriousness and causality and confirm expectedness of SAEs. 3. Immediate review of all SUSARs and life threatening or fatal SAEs/SARs that begin within 24 hours of IV iron infusion. 4. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR). 5. Using definitions in this protocol, confirm events of special interest or potential endpoints	Any SAE assigned by the PI or delegate and by the CI/Sponsor as both suspected to be related (possibly, probably or definitely) to the IMP treatment and unexpected (i.e. not documented as an expected reaction to the IMP in the RSI) will be classified as a SUSAR. Such events are subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's assessment of causality both opinions will be provided on the report. 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. 9.6 Oversight of events excluded from expedited reporting SAEs not subject to expedited reporting will be coded and	

Protocol page	V5.0 text	V6.0 text	Reason for change
	Sponsor: 1. Central data collection and verification of AEs, SAEs, SARs and SUSARs according to the trial protocol 2. Reporting safety information to the CI or delegate for the ongoing assessment of the risk / benefit 3. Assessment and confirmation of expectedness for all reported SARs 4. Reporting safety information to the independent oversight committees identified for the trial (Independent Data Monitoring Committee (IDMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan. 5. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines. 6. Notifying Investigators of SUSARs that occur within the trial. 7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial. 8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC. Trial Steering Committee: In accordance with the Charter for the TSC, periodically reviewing recruitment and the overall progress of the trial and liaising with the IDMC and sponsor regarding safety issues. Independent Data Monitoring Committee: In accordance with the Charter for the IDMC, periodically	summarised. These events are subject to statistical monitoring and review by the independent data monitoring committee and trial steering committees assigned to the trial. Where potential trends are identified by the IDMC, TSC or statistical monitoring further events may be considered subject to expedited reporting to the Sponsor and Regulatory authorities. Where a Serious Adverse Event is initially not subject to Sponsor review but later becomes reportable under sponsor requirements the Date of Sponsor Awareness will be the date there is any indication that the event is linked to administration of IMP. For example, a cardiovascular hospitalisation initially reported as unrelated to IMP that upon further clinical review is considered related to treatment). 9.7 Assessment of Record Linkage reported Serious Adverse Events Previously unreported SAEs identified via record linkage will be recorded/reported in line with section 9.4. 9.8 Responsibilities for Safety Reporting and Review This section details the responsibilities for reporting and reviewing safety information arising from the trial. Principal Investigator (PI):	

Protocol page	V5.0 text	V6.0 text	Reason for change
	reviewing unblinded safety data in individual cases and to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis, reporting concerns to the TSC and sponsor. Clinical Endpoint Committee (CEC): In accordance with the Charter for the CEC, review and classify all potential clinical endpoints in the study.	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) 1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit. 2. Using medical judgement, confirm seriousness and causality and confirm expectedness of SAEs. 3. Immediate review of all SUSARs and life threatening or fatal SAEs/SARs that begin within 24 hours of IV iron infusion. 4. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR). 5. Using definitions in this protocol, confirm events of special interest or potential endpoints	

Protocol page	V5.0 text	V6.0 text	Reason for change
		Sponsor: 1. Central data collection and verification of AEs, SAEs, SARs and SUSARs according to the trial protocol 2. Reporting safety information to the CI or delegate for the ongoing assessment of the risk / benefit 3. Assessment and confirmation of expectedness for all reported SARs 4. Reporting safety information to the independent oversight committees identified for the trial (Independent Data Monitoring Committee (IDMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan. 5. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines. 6. Notifying Investigators of SUSARs that occur within the trial. 7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial. 8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC. Trial Steering Committee: In accordance with the Charter for the TSC, periodically reviewing recruitment and the overall progress of the trial and liaising with the IDMC and	

Protocol page	V5.0 text	V6.0 text	Reason for change
		sponsor regarding safety issues. Independent Data Monitoring Committee: In accordance with the Charter for the IDMC, periodically reviewing unblinded safety data in individual cases and to determine patterns and trends of events, or identify safety issues, which would not be apparent on an individual case basis, reporting concerns to the TSC and sponsor. Clinical Endpoint Committee (CEC): In accordance with the Charter for the CEC, review and classify all potential clinical endpoints in the study.	
63	9.5 Pregnancy reporting	9.9 Pregnancy reporting	Renumbering of section
63	9.6 Overdose The ferric derisomaltose in Monofer® has a low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing. However any IMP dose which is not administered in accordance with the protocol should be reported to the sponsor. If an SAE is associated with an overdose ensure that the overdose if fully described in the SAE report form.	9.10 Overdose Ferric derisomaltose has a low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing. However, any IMP dose which is not administered in accordance with the protocol should be reported to the sponsor. If an SAE is associated with an overdose, ensure that the overdose is fully described in the SAE report form.	Minor grammatical changes
64	9.7 Reporting urgent safety measures	9.11 Reporting urgent safety measures	Renumbering of section
64	9.8 The type and duration of the follow-up of participants after adverse events.	9.12 The type and duration of the follow-up of participants after adverse events.	Renumbering of section
64	9.9 Development safety update reports	9.13 Development safety update reports	Renumbering of section

Protocol page	V5.0 text	V6.0 text	Reason for change
66	Because of the potential impact of the COVID 19 pandemic on the study results, a sensitivity analysis will be conducted excluding events occurring during the main period of the pandemic.	A primary COVID-19 analysis will be carried out on the primary endpoint and secondary endpoints, in an attempt to minimise the impact of the COVID-19 pandemic. This will include all patients randomised until the end of March 2020 with a censoring date of 30 Sept 2020. Additional sensitivity analysis will be carried involve the use of time varying treatment effects to investigate the impact of the COVID-19 pandemic on the results of the study. Time will be divided into 5 periods; pre first lockdown in the UK, first lockdown until end of first lockdown, end of first lockdown until start of second lockdown, start of second lockdown until end of second lockdown, and end of second lockdown until end of defined patient follow-up.	This modification provides some additional details of analyses that will be conducted to assess the impact of the COVID 19 pandemic on the final study results.
66	Categorical variables: - Sex, recruitment in versus out of hospital, patients taking/not taking hypoglycaemic therapy, TSAT <20% versus ferritin <100ug/L with TSAT ≥20%, aetiology of heart failure.	Categorical variables: - Sex, recruitment in versus out of hospital, patients taking/not taking hypoglycaemic therapy, TSAT <20% versus ferritin <100ug/L with TSAT ≥20%, aetiology of heart failure, CKD (eGFR <=60 ml/min/1.73m^2) versus no CKD.	Additional analysis requested by the Trial Steering Committee.
81	*Appendix 4 – Amendment History*	*Appendix 4 – Amendment History* – updated	Updated with details of protocol v6.0

EFFECTIVENESS OF INTRAVENOUS IRON TREATMENT VS STANDARD CARE IN PATIENTS WITH HEART FAILURE AND IRON DEFICIENCY: A RANDOMISED, OPEN-LABEL MULTICENTRE TRIAL

(IRONMAN)

FINAL ANALYSIS – STATISTICAL ANALYSIS PLAN

Study Title:	Effectiveness of Intravenous iron treatment vs standard care in patients with heart failure and iron deficiency: a randomised, open-label multicentre trial
Short Title:	IRONMAN
IDs:	EudraCT Number: 2015-004196-73 Sponsor's number: GN15CA190
Funded by:	British Heart Foundation
Protocol Version:	Version 5.0 (16th December 2020)

SAP Version:	Version1.0	Date:	21 DEC 2021

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	University of Glasgow		
Principal Investigator	Professor Paul Kalra	_____	_____

CONTENTS

1. INTRODUCTION

1.1 STUDY BACKGROUND

Heart failure, acute and chronic, imposes a major burden on patients, their family and carers and on the NHS. Early readmission rates are high and quality of life often markedly impaired. Many patients with chronic heart failure (CHF) are anaemic (30-50% depending on the cohort studied), and low haemoglobin is associated with increased rates of heart failure hospitalisation and mortality. Iron deficiency is also common in CHF patients whether (50-57%) or not (20-32%) they have anaemia and is associated with increased mortality, independent of the presence of anaemia.

Several small, short-term studies suggest that intravenous (IV) iron improves symptoms, reduces N-terminal pro B-type natriuretic peptide (NT-proBNP) levels and increases left ventricular ejection fraction (LVEF) in patients with CHF and iron deficiency anaemia.

Major gaps in our knowledge remain, including the impact of iron repletion on hospitalisation for heart failure, overall hospitalisation (an index of both morbidity and cost) and cardiovascular (CV) mortality as well as safety.

1.2 STUDY OBJECTIVES

To assess whether the addition of IV ferric derisomaltose to guideline-indicated therapy for CHF reduces morbidity and mortality in patients with iron deficiency and is cost-effective.

1.3 STUDY DESIGN

The trial has a prospective, randomised, open-label, blinded endpoint (PROBE) design. Patients will be individually randomised to one of two parallel groups – the addition of IV ferric derisomaltose to guideline-indicated therapy, or guideline indicated therapy alone (usual care).

1.4 RANDOMISATION

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.

1.5 SAMPLE SIZE AND POWER

The anticipated primary endpoint rate in the control group was 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 based them on a time to first event analysis using the Wald statistic in a Cox proportional hazards model. We estimated that 570 patients per group (yielding 631 first events) would provide 80% power to detect a hazard ratio of 0.8.). All efficacy analyses will be conducted on an intention to treat basis. We anticipated 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 intended to recruit 650 patients per group. Recruitment of a lower risk than expected population (mainly stable outpatients), slow recruitment and the

impact of the COVID-19 pandemic, required a reassessment of the study sample size and power. Results of the AFFIRM-HF trial and a meta-analysis of previous smaller studies suggested that a target hazard ratio of 0.75 might be appropriate, requiring 379 first primary endpoints for 80% power. We therefore decided to stop randomisations when we were confident that 379 first primary endpoints would be accrued.

1.6 Statistical Analysis Plan (SAP)

1.6.1 SAP Objectives

The objective of this SAP is to describe the statistical analyses to be carried out for the IRONMAN final analysis. Analyses of the IRONMAN biobank sub-study, economic analyses and post end of study record linkage are not covered by this SAP.

The current version of the protocol at the time of writing is version 5 dated 16th December 2020. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. This will be documented as part of the Robertson Centre Change Impact Assessment processes.

1.6.2 General principles

Summaries for continuous variables, unless stated otherwise, will consist of number of values, number missing, mean, standard deviation, median, lower and upper quartiles, minimum and maximum. Summaries for categorical variables will consist of number of values, number missing and percentages. Summaries for count data will consist of number of values, number missing, number of events and rates (calculated as counts per 100 patient years of follow-up).

All treatment comparisons will be calculated as IV iron relative to usual care.

1.6.3 Deviations to those specified in the protocol

The secondary endpoints have been reordered. The time periods for the analysis of days dead and out of hospital have been amended to account for the wide variation in follow-up.

1.6.4 Additional analyses to those specified in the protocol

A hierarchical analysis of secondary endpoints has been introduced. Additional subgroup analyses have been introduced, as has a primary COVID-19 analysis.

1.6.5 Software

Analyses will be conducted using SAS for Windows v 9.4, or higher and R version 3.6.0 or higher.

2. Analysis

2.1 Study Populations

All efficacy analyses will be carried out in the intention-to-treat (ITT) population of all validly randomised patients. The ITT population will exclude patients, if any, where there is valid evidence that they were randomised in error.

The Safety Population will consist of all patients in the usual care arm, and all patients in the IV Iron arm who received at least one infusion of IV Iron.

2.2 End of Follow-up and Censoring Process for Efficacy Analysis

All efficacy analyses will be carried out in the ITT population. The ITT analysis will censor patients after death from any cause not included in the endpoint being considered, date of withdrawal of consent for all further follow-up in the study, or defined end of study follow-up date, whichever occurs first.

2.3 Study Status

The numbers of patients consented and screened, excluded during screening or unwilling to be randomised, and randomised, will be summarised. Of those randomised, the numbers withdrawing consent for all further study follow-up (excluding death as a reason), from attending study visits, the numbers who die and the numbers completing the study alive will be described. Time in the study (from randomisation until end of study follow-up [death, withdrawal of consent for all follow-up, or defined end of follow-up date]) will also be summarised.

Time to withdrawal of consent for all follow-up from the study (not including death as a reason) will be described by cumulative incidence functions (split by randomised treatment). Reasons for withdrawal of consent for all follow-up will be summarised by randomised treatment group.

Attendance at each study visit (attended in person, attended remotely, missed visit, withdrawn from study, withdrawn from attending study visits, or died) will be summarised.

The number of patients in the safety set will be summarised.

In the group randomised to receive IV Iron, the percentage of patients infused at each visit among those who have not died or completely withdrawn consent, will be plotted over time.

2.4 Protocol Deviations

The protocol deviations will be categorised and the categories (major, minor etc.) summarised.

2.5 Baseline Characteristics

The following baseline information will be summarised for the randomised population by treatment group:

Demographics

- Age
- Gender
- Ethnic group: white/black/asian/other
- Smoking status: current/former/never
- Recruitment status: hospitalised, hospitalisation within last 6 months, stable outpatient

Heart failure related history

- Aetiology (ischaemic, dilated cardiomyopathy, hypertension, valve disease, congenital, other – specify, unknown)
- History of atrial fibrillation or flutter: Y/N
- LVEF: value and modality (echo, cardiac magnetic resonance imaging, left ventricular angiogram, other – specify)
- Duration of heart failure: specify - new diagnosis, <= 1 year, >1 year
- Prior heart failure hospitalisation (including previous admission for those patients who are currently hospitalised): never, >1 year, 6-12 months, < 6 months

Co-morbidities

- Hypertension: Y/N
- Inflammatory disease: Y/N
- Rheumatoid arthritis Y/N,
- Inflammatory bowel disease Y/N
- Inflammatory disease other Y/N
- Gastrointestinal (GI) tract pathology Y/N
- History of peptic ulcer Y/N
- History of cancer Y/N
- Diverticular disease Y/N
- GI tract pathology other Y/N

- Diagnosis of cancer in last 5 years: Y/N.
- Chronic obstructive pulmonary disease (COPD): Y/N
- Asthma: Y/N
- Diabetes: Type1/Type2/N

Other CV history

- Acute coronary event (prior MI) – never, <1 year, 1-5 years, >5 years
- CABG – never, <1 year, 1-5 years, >5 years
- PCI – never, <1 year, 1-5 years, >5 years
- Device – never, <1 year, 1-5 years, >5 years
- Type of device - ICD, PPM, CRT-P, CRT-D
- Valve Surgery – never, <1 year, 1-5 years, >5 years
- Type of valve surgery – mechanical, bio-prosthetic
- Primary valvular disease – never, <1 year, 1-5 years, >5 years
- Type of valvular disease – aortic, mitral
- Stroke – never, <1 year, 1-5 years, >5 years

Assessments

- SBP
- DBP
- Height
- Weight
- BMI
- Oedema: Absent, minor (feet/ankles), moderate (lower legs), severe (thighs/sacrum)
- NYHA: II/III/IV

Heart failure drugs

- loop diuretic: Y/N
- thiazide like diuretic: Y/N
- ACE inhibitor: Y/N

- ARB: Y/N
- ACE or ARB: Y/N
- beta-blocker: Y/N
- digoxin: Y/N
- mineralocorticoid receptor antagonist: Y/N
- sacubitril valsartan: Y/N
- ivabradine: Y/N

Drugs for diabetes

- Any diabetes drug: Y/N
- Insulin: Y/N
- Metformin: Y/N
- Sulphonylureas: Y/N
- SGLT2 inhibitor: Y/N
- Other: Y/N

Other drugs

- Treatment for COPD/asthma: Y/N,
- Aspirin: Y/N (prescribed or OC)
- Other anti-platelet agents: Y/N
- NSAIDs: Y/N (prescribed or OC)
- Proton pump inhibitors: Y/N
- H-2 antagonists: Y/N
- Anti-coagulants: Y/N
- Steroids: Y/N
- Oral iron: Y/N

ECG

- AF
- sinus rhythm

- paced
- heart rate
- QRS duration
- (if QRS>120 ms: left bundle branch block, right bundle branch block, interventricular conduction delay, paced)

Blood analyses

- TSAT
- Ferritin
- creatinine,
- eGFR (MDRD and CKD-EPI)
- CRP
- Haemoglobin
- platelets
- MCV
- MCHC
- MCH
- Sodium
- Potassium
- RDW*
- Bilirubin*
- Albumin*
- Random glucose*
- BNP** (overall and by rhythm status)
- NTproBNP** (overall and by rhythm status)

*Only recorded if available, ** where required for inclusion.

QoL scores

- EQ5D VAS

- EQ5D index
- EQ5D (each of the 5 dimensions)
- MLwHF overall score
- MLwHF physical score
- MLwHF emotional score

6MWT

- Distance
- Reasons for noncompletion

Baseline characteristics will be compared between randomised groups using chi-square statistics (or Fishers Exact test) for categorical variables and Wilcoxon rank sum tests for continuous variables. These tests are sometimes required by journals.

2.6 EFFICACY ENDPOINTS

All efficacy analyses will be carried out in the ITT population.

2.6.1 PRIMARY ENDPOINT

The primary outcome is the composite of cardiovascular death and hospitalisations for heart failure. Hospitalisations for heart failure will consist of events where heart failure is adjudicated to be the primary or a contributory reason for admission. In recurrent event analysis of the composite of cardiovascular death and hospitalisations for heart failure, it is important not to double count events and to make events, as far as is possible, independent within a patient. To this end, hospitalisations for heart failure during which the patient dies of cardiovascular causes will be counted as a single event. In addition, any hospitalisation for heart failure where the patient is readmitted for heart failure on the day of discharge will be counted as a single event.

The primary analysis will be on the outcome of CV death and hospitalisations for heart failure, analysed as recurrent events.

A recurrent even analysis will be carried out for the primary endpoint, using the method of Lin, Wei, Yang and Ying [1] including the randomised treatment group and recruitment context (stratification variable) as covariates. From this model, the estimated treatment effect, 95% confidence interval and p-value from the Wald statistic will be presented. A marginal mean function for the cumulative number of recurrent events over time, split by randomised treatment group, will be produced (Ghosh and Lin [2]). The numbers of patients with first events, crude percentage of patients with first events, rates of events /100 patient years of follow-up and the distribution of the numbers of events per patient will be summarised by treatment group.

2.6.2 SUBGROUP ANALYSES

Subgroup analyses will be carried out for the primary endpoint, analysed as a recurrent event and separately analysed as time to first event. For each of the baseline covariates noted below, p-values for the test of the interaction between the variable defining the subgroup and randomised treatment allocation will be derived using the Wald statistic. Forest plots will be produced for the subgroup analyses results (for time to first event and recurrent events separately).
Categorical variables:

- Sex,
- Recruitment in hospital, recent discharges, stable outpatients with raised BNP or NTproBNP,
- Patients taking/not taking hypoglycaemic therapy,
- TSAT <20% versus ferritin <100ug/L with TSAT ≥20%,
- Aetiology of heart failure. (ischaemic vs non-ischaemic),
- NYHA (II vs III/IV),
- Duration of heart failure (new/<=1 year/>1 year),
- eGFR <=60 vs >60 (calculated by CKD-EPI),
- WHO anaemia definition (non-anaemic ≥12.0 women/≥13.0 men, mild – 11.0-11.9 women/11.0-12.9 men, moderate – 8.0-10.9).

Continuously distributed variables by thirds of their distributions of baseline:

- TSAT,
- Ferritin,
- Haemoglobin (after adding 1 to the levels for females)
- age,
- eGFR (calculated by CKD-EPI),
- Systolic blood pressure,
- LVEF

2.6.3 SECONDARY ENDPOINTS

The following are the secondary endpoints listed in the order in which they will be analysed in a hierarchical fashion if the primary analysis is significant at the 5% level. Endpoints in the list will continue to be tested at the 5% significance level until the first event is not significant. All previous endpoints will be considered statistically significantly affected by randomised treatment.

1. Hospitalisation for worsening heart failure (recurrent events).
2. CV hospitalisation (first event)
3. CV death or hospitalisation for heart failure analysed as time to first event.
4. Overall Score from Minnesota Living with Heart Failure at 4 months

5. Cardiovascular mortality
6. Overall EQ5D VAS at 4 months
7. Overall EQ5D index at 4 months
8. CV mortality or hospitalisation for major CV event (stroke, MI, heart failure) (first event)
9. All-cause mortality
10. All-cause hospitalisation (first event)
11. Combined all-cause mortality or first all-cause unplanned hospitalisation
12. Physical domain of QoL (Minnesota Living With Heart Failure) at 4 months
13. Physical domain of QoL (Minnesota Living With Heart Failure) at 20 months
14. Overall EQ-5D VAS at 20 months
15. Overall EQ-5D index at 20 months
16. Overall Score from Minnesota Living with Heart Failure at 20 months
17. Days dead or hospitalised at 3 years
18. Quality-adjusted days alive and out of hospital at 3 years
19. 6-minute walk test at 4 months
20. 6-minute walk test at 20 months

Power calculations have been carried out for the first four secondary endpoints. For the endpoint of hospitalisation for worsening heart failure there will be 80% power to detect a hazard ratio of 0.71 (based on a time to first event calculation) assuming at least 268 first events. For the endpoint of cardiovascular hospitalisation there will be 80% power to detect a hazard ratio of 0.76 assuming at least 417 first events. For the endpoint of cardiovascular death or heart failure hospitalisation there will be 80% power to detect a hazard ratio of 0.75 assuming at least 379 first events. For the Minnesota Living with Heart Failure total score at 4 months there will be at least 80% power to detect a difference in mean scores of 4.5 assuming a common standard deviation of 24 and at least 450 subjects in each group with data.

Secondary endpoints involving recurrent events will be analysed as for the primary endpoint, with corresponding adjustments to reduce the risk of double counting events. Secondary endpoints involving time to first event outcomes will be analysed using Cox proportional hazards models including treatment effect and stratification variables, with the treatment effect hazard ratio and 95% confidence intervals estimated with associated p-values using the Wald statistic. Treatment groups will be compared graphically using Ghosh and Lin plots for recurrent events and using cumulative incidence functions adjusting for the competing risk of fatal events not included in the endpoint, for time to first event analyses. Forest plots will be

produced for the primary and secondary time to event analyses results (for time to first event and recurrent events separately).

QoL scores and 6-minute walk tests results will be compared between randomised treatment groups at 4 and 20 months using ANCOVA, with treatment group and stratification variable as covariates. For patients recruited as stable outpatients, these analyses will be repeated adjusting for baseline levels, in those patients whose baseline data are available. These analyses will be repeated using a multiple imputation procedure to account for missing data post-baseline.

Missing values will be imputed within each treatment group separately using SAS PROC MI adjusting for baseline levels and the stratification variable. Fifty datasets will be generated and results analysed by ANCOVA within each dataset and results combined using Rubin's rules using the SAS PROC MIANALYZE procedure.

In addition, EQ5D visual analogue scores and EQ5D indices will be summarised at each timepoint assessed with changes from baseline. For each of EQ5D visual analogue score and EQ5D index, a mixed effects repeated measures model with a general covariance matrix and including treatment main effect, study visit and stratification variable, will be used to estimate the average treatment effect over time. In a second analysis, a heterogeneous treatment effect over time will be investigated by adding a treatment by study visit interaction to the model.

Mean days dead or hospitalised at 1 year, 2 years and overall and mean quality-adjusted days alive and out of hospital at 1 year, 2 years and overall will be compared between treatment groups using a bootstrap analysis. The analyses will scale each patient's results by the potential length of follow-up.

2.6.4 SENSITIVITY ANALYSES

The primary endpoint analysis will be repeated using a joint frailty model for CV mortality and hospitalisations for worsening heart failure [3]. This will provide estimates separately of the treatment effects for CV death and recurrent hospitalisation for heart failure, and of a weighted combination of these estimates with weights corresponding to the numbers of each type of event. A similar approach will be taken using the using the method of Mao and Lin [4]. In the analyses of the composite primary endpoint, deaths and heart failure hospitalisations will be weighted by their frequency.

A primary COVID-19 analysis will be carried out on the primary endpoint and secondary endpoints, in an attempt to minimise the impact of the COVID-19 pandemic. This will include all patients randomised until the end of March 2020 with a censoring date of 30 Sept 2020. This decision reflects the fact that IV iron administered prior to the initial lockdown would be expected to have effects persisting for at least six months Additional sensitivity analysis will use time-varying treatment effects to investigate the impact of the COVID-19 pandemic on the results of the study. Time will be divided into 5 periods; pre first lockdown in the UK, start of first lockdown until end of first lockdown, end of first lockdown until start of second lockdown, start of second lockdown until end of second lockdown, and end of second lockdown until end of defined patient follow-up. This will permit, in a descriptive fashion, the estimation of treatment effects in each period and the comparison of effects in lockdown and non-lockdown periods.

2.6.5 Additional analyses

The number of non-SAE blood transfusions and rates per 100 patient years will be summarised overall and by reason (trauma, surgery, haemorrhage and anaemia). The rates of transfusions will be compared between treatment arms using a negative binomial model adjusted for stratification variable and with log follow-up time as an offset. The rate ratio, 95% CI and p-value will be calculated.

The number and rate of non-SAE haemorrhages (per 100 patient years) will be summarised split by treatment arm, overall and by site (upper GI, lower GI, GI bleed, GU bleed, other bleed) and by severity (major, minor).

To help understand the mechanism of any potential benefit of IV iron on the described endpoints, we will compare haemoglobin, platelets, serum creatinine and eGFR between the randomised treatment groups at 4 months and 20 months, with all but platelets also assessed at the patient's last measurement.

The adjudications by the endpoints committee for non-fatal SAEs and causes of death will be summarised in the ITT population.

SBP, DBP, heart rate, weight and BMI and changes from baseline will be summarised over time. Mean levels and mean changes with associated 95% CIs will be plotted by study visit split be treatment group.

The numbers and percentages with oedema and distribution of NYHA class will be summarised and plotted over time.

2.6.6 Assumption Checking

The proportional hazards/means assumption for the primary outcome will be tested informally by review of the cumulative incidence plots, and formally by adding a log(time)*treatment covariate in the relevant models and assessing its statistical significance at the 5% significance level. If the extent of any deviation from proportional hazards is minor, the proportional hazards/means model results will be reported with a caveat that the hazard ratio represents approximately the average treatment effect over the follow-up period. If there is more extensive deviation, for instance clear evidence of the survival curves crossing, a further analysis will be stratified with appropriate time intervals.

2.7 Safety Outcomes

Safety outcomes post randomisation will be presented for the safety population, that is the randomised population excluding those in the IV iron arm where we have clear evidence that no study IV iron was received. Patients omitted from the safety analysis will have their serious adverse event (SAE) data listed.

2.7.1 Analysis Periods

The safety analyses will be carried out in the Safety population for the following follow-up period:

- Within Study - randomisation until date of death/withdrawal of consent for all further study follow-up or end of defined study follow-up date (whichever comes first)

There will be no on-treatment reporting of safety events in this study, in part because you can only withdraw from one study arm. In addition, it is difficult to define the on-treatment period for this study, as treatment is only given when required and because the effect of the treatment is long lasting. We also note the concerns that have been expressed about on-treatment SAE analyses [5].

2.7.2 TIME TO EVENT SAFETY ENDPOINTS

The following safety endpoints, Within Study, will be analysed in the same way as the efficacy time to first event endpoints:

- Death due to infection
- Hospitalisation primarily for infection (first event)

2.7.3 TREATMENT EXPOSURE

In the IV iron arm, for each study visit, we will summarise the number of patients who could potentially have attended, the number attending remotely, the number attending face-to-face, the number infused with IV iron, and for those infused, summarise the doses infused. Summarise overall the distribution of the numbers of infusions received per patient and the total dose received.

2.7.4 SAEs, SAEs RESULTING IN DEATH, DEATHS

SAEs and SAEs resulting in death will be summarised Within Study by treatment group, by system organ class and preferred term as classified by MedDRA (version 23.0). In addition, tabulation of SAEs will be repeated for events considered severe, and in the IV iron arm for those considered to be at least possibly related to study drug and for those leading to permanent withdrawal from study drug. Additional tables will be produced for the system organ classes with 95% confidence intervals (and p-values) for the differences in proportions and differences in rates in the treatment groups. Tables of preferred terms reported by more than 3% of the randomised population will also be produced. The total number of events, numbers of patients with first events, crude % of patients with events, rates of events /100 patient years of follow-up will be summarised by treatment group.

A table of any SUSARs (serious unexpected serious adverse reactions) will be produced.

The distribution of the total number of events will be reported for each category of outcome, action and severity.

Adjudicated causes of death will be summarised by treatment group in the safety population.

A cumulative incidence plot Within Study split by treatment group will be produced for the time to first serious adverse event.

2.7.5 LABORATORY VALUES

Laboratory values and changes from baseline will be summarised in tables and plotted using box and whisker plots and using means and 95% CIs. Results may be transformed as appropriate.

Summaries will be provided, by treatment group, for the numbers and percentage of subjects with any post-baseline laboratory values of clinical concern:

- eGFR: < 30
- Hamoglobin: <11 (men)/<10 (women)
- MCV: <80 or >100
- MCHC: <30
- MCH: <26
- Platelets: <100
- Sodium: <135
- Potassium: <3.5 or >5.5
- Urea: >20
- CRP: >20

2.7.6 CONCOMITANT MEDICATIONS

The number and percentage of patients reporting use of common concomitant medications during the post-baseline period will be summarised using the checklist classification in the eCRF.

3. TABLES AND FIGURES

Dummy reports will be produced and reviewed by the chief investigator. Approval of the content of the final statistical outputs will be documented prior to database lock.

4. LISTINGS

Listings of all derived datasets will be produced as excel spreadsheets. In addition, listings will be produced containing the information used for each output table and figure in the report.

Any listings required for a regulatory submission will be produced after database lock.

5. REFERENCES

1. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. J R Stat Soc B 2000; 62: 711-30.
2. Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. Biometrics 2000; 56: 554-62.
3. Y. Mazroui, S. Mathoulin-Pelissier, P. Soubeyranb and V. Rondeau (2012) General joint frailty model for recurrent event data with a dependent terminal event: Application to follicular lymphoma data. Statistics in Medicine, 31, 11-12, 1162-1176.4. Mao L, Lin DY. Semiparametric regression for the weighted composite endpoint of recurrent and terminal events. Biostatistics 2016; 17:390-403.

5. Yang F, Wittes J, Pitt B. Beware of on-treatment safety analyses. Clin Trials. 2019; 16 :63-70.

6. DOCUMENT HISTORY

This is the first version of the SAP, initial creation.

EFFECTIVENESS OF INTRAVENOUS IRON TREATMENT VS STANDARD CARE IN PATIENTS WITH HEART FAILURE AND IRON DEFICIENCY: A RANDOMISED, OPEN-LABEL MULTICENTRE TRIAL

(IRONMAN)

FINAL ANALYSIS – STATISTICAL ANALYSIS PLAN

Study Title:	Effectiveness of Intravenous iron treatment vs standard care in patients with heart failure and iron deficiency: a randomised, open-label multicentre trial
Short Title:	IRONMAN
IDs:	EudraCT Number: 2015-004196-73 Sponsor's number: GN15CA190
Funded by:	British Heart Foundation
Protocol Version:	Version 6.0 (15th December 2021)

SAP Version: Version2.0 Date: 01 JUL 2022

		Signature	Date
Prepared by:	Michele Robertson Assistant Director Commercial Biostatistics Robertson Centre for Biostatistics University of Glasgow		

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	Robertson Centre for Biostatistics		
	University of Glasgow		
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Principal Investigator	Professor Paul Kalra	_____	_____

CONTENTS

1. INTRODUCTION

1.1 STUDY BACKGROUND

Heart failure, acute and chronic, imposes a major burden on patients, their family and carers and on the NHS. Early readmission rates are high and quality of life often markedly impaired. Many patients with chronic heart failure (CHF) are anaemic (30-50% depending on the cohort studied), and low haemoglobin is associated with increased rates of heart failure hospitalisation and mortality. Iron deficiency is also common in CHF patients whether (50-57%) or not (20-32%) they have anaemia and is associated with increased mortality, independent of the presence of anaemia.

Several small, short-term studies suggest that intravenous (IV) iron improves symptoms, reduces N-terminal pro B-type natriuretic peptide (NT-proBNP) levels and increases left ventricular ejection fraction (LVEF) in patients with CHF and iron deficiency anaemia.

Major gaps in our knowledge remain, including the impact of iron repletion on hospitalisation for heart failure, overall hospitalisation (an index of both morbidity and cost) and cardiovascular (CV) mortality as well as safety.

1.2 STUDY OBJECTIVES

To assess whether the addition of IV ferric derisomaltose to guideline-indicated therapy for CHF reduces morbidity and mortality in patients with iron deficiency and is cost-effective.

1.3 STUDY DESIGN

The trial has a prospective, randomised, open-label, blinded endpoint (PROBE) design. Patients will be individually randomised to one of two parallel groups – the addition of IV ferric derisomaltose to guideline-indicated therapy, or guideline indicated therapy alone (usual care).

1.4 RANDOMISATION

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.

1.5 SAMPLE SIZE AND POWER

The anticipated primary endpoint rate in the control group was 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 based them on a time to first event analysis using the Wald statistic in a Cox proportional hazards model. We estimated that 570 patients per group (yielding 631 first events) would provide 80% power to detect a hazard ratio of 0.8.). All efficacy analyses will be conducted on an intention to treat basis. We anticipated 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 intended to recruit 650 patients per group. Recruitment of a lower risk than expected population (mainly stable outpatients), slow recruitment and the

impact of the COVID-19 pandemic, required a reassessment of the study sample size and power. Results of the AFFIRM-HF trial and a meta-analysis of previous smaller studies suggested that a target hazard ratio of 0.75 might be appropriate, requiring 379 first primary endpoints for 80% power. We therefore decided to stop randomisations when we were confident that 379 first primary endpoints would be accrued.

1.6 Statistical Analysis Plan (SAP)

1.6.1 SAP Objectives

The objective of this SAP is to describe the statistical analyses to be carried out for the IRONMAN final analysis. Analyses of the IRONMAN biobank sub-study, economic analyses and post end of study record linkage are not covered by this SAP.

The current version of the protocol at the time of writing is version 5 dated 16th December 2020. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. This will be documented as part of the Robertson Centre Change Impact Assessment processes.

1.6.2 General principles

Summaries for continuous variables, unless stated otherwise, will consist of number of values, number missing, mean, standard deviation, median, lower and upper quartiles, minimum and maximum. Summaries for categorical variables will consist of number of values, number missing and percentages. Summaries for count data will consist of number of values, number missing, number of events and rates (calculated as counts per 100 patient years of follow-up).

All treatment comparisons will be calculated as IV iron relative to usual care.

1.6.3 Deviations/Additional analyses to those specified in the protocol

The secondary endpoints have been reordered. The time periods for the analysis of quality adjusted days alive and out of hospital have been amended to account for the limited availability of long-term NYHA data associated with the COVID-19 pandemic. The repeated measures analysis of EQ5D data will be limited to the first 3 years for the same reason (COVID-19).

A hierarchical analysis of secondary endpoints has been introduced. Additional subgroup analyses have been introduced (NYHA, duration of heart failure, anaemia and ferritin).

1.6.4 Software

Analyses will be conducted using SAS for Windows v 9.4, or higher and R version 3.6.0 or higher.

2. Analysis

2.1 Study Populations

All efficacy analyses will be carried out in the intention-to-treat (ITT) population of all validly randomised patients. The ITT population will exclude patients, if any, where there is valid evidence that they were randomised in error.

The Safety Population will consist of all patients in the usual care arm, and all patients in the IV Iron arm who received at least one infusion of IV Iron.

2.2 End of Follow-up and Censoring Process for Efficacy Analysis

All efficacy analyses will be carried out in the ITT population. The ITT analysis will censor patients after death from any cause not included in the endpoint being considered, date of withdrawal of consent for all further follow-up in the study, or defined end of study follow-up date, whichever occurs first.

2.3 Study Status

The numbers of patients consented and screened, and the number validly randomised will be summarised. Of those who did not progress to a valid randomisation, the reason will be summarised. Of those with a valid randomisation, the numbers withdrawing consent for all further study follow-up (excluding death as a reason), the numbers who die and the numbers completing the study alive will be described. Time in the study (from randomisation until end of study follow-up [death, withdrawal of consent for all follow-up, or defined end of follow-up date]) will also be summarised.

Time to withdrawal of consent for all follow-up from the study (not including death as a reason) will be described by cumulative incidence functions (split by randomised treatment). Reasons for withdrawal of consent for all follow-up will be summarised by randomised treatment group.

Attendance at each study visit (attended in person, attended remotely, missed visit, withdrawn from study, withdrawn from attending study visits, or died) will be summarised.

The number of patients in the safety set will be summarised.

In the group randomised to receive IV Iron, the percentage of patients infused at each visit among those who have not died or completely withdrawn consent, will be plotted over time.

2.4 Protocol Deviations

The protocol deviations will be categorised and the categories (major, minor etc.) summarised.

2.5 Baseline Characteristics

The following baseline information will be summarised for the randomised population by treatment group:

Demographics

- Age
- Gender
- Ethnic group: white/black/asian/other
- Smoking status: current/former/never
- Recruitment status: hospitalised, hospitalisation within last 6 months, stable outpatient

Heart failure related history

- Aetiology (ischaemic, dilated cardiomyopathy, hypertension, valve disease, congenital, other – specify, unknown)
- History of atrial fibrillation or flutter: Y/N
- LVEF: value and modality (echo, cardiac magnetic resonance imaging, left ventricular angiogram, other – specify)
- Duration of heart failure: specify - new diagnosis, <= 1 year, >1 year
- Prior heart failure hospitalisation (including previous admission for those patients who are currently hospitalised): never, >1 year, 6-12 months, < 6 months

Co-morbidities

- Hypertension: Y/N
- Inflammatory disease: Y/N
- Rheumatoid arthritis Y/N,
- Inflammatory bowel disease Y/N
- Inflammatory disease other Y/N
- Gastrointestinal (GI) tract pathology Y/N
- History of peptic ulcer Y/N
- History of cancer Y/N
- Diverticular disease Y/N

- GI tract pathology other Y/N
- Diagnosis of cancer in last 5 years: Y/N.
- Chronic obstructive pulmonary disease (COPD): Y/N
- Asthma: Y/N
- Diabetes: Type1/Type2/N

Other CV history

- Acute coronary event (prior MI) – never, <1 year, 1-5 years, >5 years
- CABG – never, <1 year, 1-5 years, >5 years
- PCI – never, <1 year, 1-5 years, >5 years
- Device – never, <1 year, 1-5 years, >5 years
- Type of device - ICD, PPM, CRT-P, CRT-D
- Valve Surgery – never, <1 year, 1-5 years, >5 years
- Type of valve surgery – mechanical, bio-prosthetic
- Primary valvular disease – never, <1 year, 1-5 years, >5 years
- Type of valvular disease – aortic, mitral
- Stroke – never, <1 year, 1-5 years, >5 years

Assessments

- SBP
- DBP
- Height
- Weight
- BMI
- Oedema: Absent, minor (feet/ankles), moderate (lower legs), severe (thighs/sacrum)
- NYHA: II/III/IV

Heart failure drugs

- loop diuretic: Y/N

- thiazide like diuretic: Y/N
- Any loop or thiazide diuretic: Y/N
- ACE inhibitor: Y/N
- ARB: Y/N
- ACE or ARB: Y/N
- beta-blocker: Y/N
- digoxin: Y/N
- mineralocorticoid receptor antagonist: Y/N
- sacubitril valsartan: Y/N
- ivabradine: Y/N

Drugs for diabetes

- Insulin: Y/N
- Metformin: Y/N
- Sulphonylureas: Y/N
- SGLT2 inhibitor: Y/N
- DDP4: Y/N
- GLP1: Y/N
- Other: Y/N

Other drugs

- Treatment for COPD/asthma: Y/N,
- Aspirin: Y/N (prescribed or OC)
- Other anti-platelet agents: Y/N
- NSAIDs: Y/N (prescribed or OC)
- Proton pump inhibitors: Y/N
- H-2 antagonists: Y/N
- Anti-coagulants: Y/N

- Steroids: Y/N
- Oral iron: Y/N

ECG

- AF
- sinus rhythm
- paced
- heart rate
- QRS duration
- (if QRS>120 ms: left bundle branch block, right bundle branch block, interventricular conduction delay, paced)

Blood analyses

- TSAT
- Ferritin
- creatinine,
- eGFR (MDRD and CKD-EPI)
- CRP
- Haemoglobin
- platelets
- MCV
- MCHC
- MCH
- Sodium
- Potassium
- Urea
- RDW*
- Bilirubin*
- Albumin*

- Random glucose*
- BNP** (overall and by rhythm status)
- NTproBNP** (overall and by rhythm status)

*Only recorded if available, ** where required for inclusion.

QoL scores

- EQ5D VAS
- EQ5D index
- EQ5D (each of the 5 dimensions)
- MLwHF overall score
- MLwHF physical score
- MLwHF emotional score

6MWT

- Distance
- Reasons for noncompletion

In addition, all baseline medications will be summarised by WHO (version Jan 2011) ATC levels 1 and 4.

Baseline characteristics will be compared between randomised groups using chi-square statistics (or Fishers Exact test) for categorical variables and Wilcoxon rank sum tests for continuous variables. These tests are sometimes required by journals.

2.6 EFFICACY ENDPOINTS

All efficacy analyses will be carried out in the ITT population.

2.6.1 PRIMARY ENDPOINT

The primary outcome is the composite of cardiovascular death and hospitalisations for heart failure. Hospitalisations for heart failure will consist of events where heart failure is adjudicated to be the primary or a contributory reason for admission. In recurrent event analysis of the composite of cardiovascular death and hospitalisations for heart failure, it is important not to double count events and to make events, as far as is possible, independent within a patient. To this end, hospitalisations for heart failure during which the patient dies of cardiovascular causes will be counted as a single event. In addition, any hospitalisation for heart failure where the patient is readmitted for heart failure on the day of discharge will be counted as a single event.

The primary analysis will be on the outcome of CV death and hospitalisations for heart failure, analysed as recurrent events.

A recurrent even analysis will be carried out for the primary endpoint, using the method of Lin, Wei, Yang and Ying [1] including the randomised treatment group and recruitment context (stratification variable) as covariates. From this model, the estimated treatment effect, 95% confidence interval and p-value from the Wald statistic will be presented. A marginal mean function for the cumulative number of recurrent events over time, split by randomised treatment group, will be produced (Ghosh and Lin [2]). The numbers of patients with first events, crude percentage of patients with first events, rates of events /100 patient years of follow-up and the distribution of the numbers of events per patient will be summarised by treatment group.

2.6.2 SUBGROUP ANALYSES

Subgroup analyses will be carried out for the primary endpoint, analysed as a recurrent event and separately analysed as time to first event. For each of the baseline covariates noted below, p-values for the test of the interaction between the variable defining the subgroup and randomised treatment allocation will be derived using the Wald statistic. Forest plots will be produced for the subgroup analyses results (for time to first event and recurrent events separately).
Categorical variables:

- Sex,
- Recruitment in hospital, recent discharges, stable outpatients with raised BNP or NTproBNP,
- Patients taking/not taking hypoglycaemic therapy,
- TSAT <20% versus ferritin <100ug/L with TSAT ≥20%,
- Aetiology of heart failure. (ischaemic vs non-ischaemic),
- NYHA (II vs III/IV),
- Duration of heart failure (new/<=1 year/>1 year),
- eGFR <=60 vs >60 (calculated by CKD-EPI),
- WHO anaemia definition (non-anaemic ≥12.0 women/≥13.0 men, mild – 11.0-11.9 women/11.0-12.9 men, moderate – 8.0-10.9).

Continuously distributed variables by thirds of their distributions of baseline:

- TSAT,
- Ferritin,
- Haemoglobin (after adding 1 to the levels for females)
- age,
- eGFR (calculated by CKD-EPI),
- Systolic blood pressure,
- LVEF

2.6.3 SECONDARY ENDPOINTS

The following are the secondary endpoints listed in the order in which they will be analysed in a hierarchical fashion if the primary analysis is significant at the 5% level. Endpoints in the list will continue to be tested at the 5% significance level until the first event is not significant. All previous endpoints will be considered statistically significantly affected by randomised treatment.

1. Hospitalisation for worsening heart failure (recurrent events).
2. CV hospitalisation (first event)
3. CV death or hospitalisation for heart failure analysed as time to first event.
4. Overall Score from Minnesota Living with Heart Failure at 4 months
5. Cardiovascular mortality
6. Overall EQ5D VAS at 4 months
7. Overall EQ5D index at 4 months
8. CV mortality or hospitalisation for major CV event (stroke, MI, heart failure) (first event)
9. All-cause mortality
10. All-cause hospitalisation (first event)
11. Combined all-cause mortality or first all-cause unplanned hospitalisation
12. Physical domain of QoL (Minnesota Living With Heart Failure) at 4 months
13. Physical domain of QoL (Minnesota Living With Heart Failure) at 20 months
14. Overall EQ-5D VAS at 20 months
15. Overall EQ-5D index at 20 months
16. Overall Score from Minnesota Living with Heart Failure at 20 months
17. Days dead or hospitalised at 3 years
18. Quality-adjusted days alive and out of hospital at 1 year
19. 6-minute walk test at 4 months
20. 6-minute walk test at 20 months

Power calculations have been carried out for the first four secondary endpoints. For the endpoint of hospitalisation for worsening heart failure there will be 80% power to detect a hazard ratio of 0.71 (based on a time to first event calculation) assuming at least 268 first

events. For the endpoint of cardiovascular hospitalisation there will be 80% power to detect a hazard ratio of 0.76 assuming at least 417 first events. For the endpoint of cardiovascular death or heart failure hospitalisation there will be 80% power to detect a hazard ratio of 0.75 assuming at least 379 first events. For the Minnesota Living with Heart Failure total score at 4 months there will be at least 80% power to detect a difference in mean scores of 4.5 assuming a common standard deviation of 24 and at least 450 subjects in each group with data.

Secondary endpoints involving recurrent events will be analysed as for the primary endpoint, with corresponding adjustments to reduce the risk of double counting events. Secondary endpoints involving time to first event outcomes will be analysed using Cox proportional hazards models including treatment effect and stratification variables, with the treatment effect hazard ratio and 95% confidence intervals estimated with associated p-values using the Wald statistic. Treatment groups will be compared graphically using Ghosh and Lin plots for recurrent events and using cumulative incidence functions adjusting for the competing risk of fatal events not included in the endpoint, for time to first event analyses. Forest plots will be produced for the primary and secondary time to event analyses results (for time to first event and recurrent events separately).

QoL scores and 6-minute walk tests results will be compared between randomised treatment groups at 4 and 20 months using ANCOVA, with treatment group and stratification variable as covariates. For patients recruited as stable outpatients, these analyses will be repeated adjusting for baseline levels, in those patients whose baseline data are available.
These analyses will be repeated using a multiple imputation procedure to account for missing data post-baseline. Missing values will be imputed within each treatment group separately using SAS PROC MI adjusting for the stratification variable. For the stable outpatient analysis, missing values will be imputed adjusting for the baseline value and stratification variable. Fifty datasets will be generated and results analysed by ANCOVA within each dataset and results combined using Rubin's rules using the SAS PROC MIANALYZE procedure.

In addition, EQ5D visual analogue scores and EQ5D indices will be summarised at each timepoint assessed with changes from baseline. For each of EQ5D visual analogue score and EQ5D index, a mixed effects repeated measures model with a general covariance matrix and including treatment main effect, study visit and stratification variable, will be used to estimate the average treatment effect over time, including data up to 3 years. In a second analysis, a heterogeneous treatment effect over time will be investigated by adding a treatment by study visit interaction to the model.

Mean days dead or hospitalised at 3 years and mean quality-adjusted days alive and out of hospital at 1 year will be compared between treatment groups using a bootstrap analysis. The analyses will scale each patient's results by the potential length of follow-up.

2.6.4 SENSITIVITY ANALYSES

The primary endpoint analysis will be repeated using a joint frailty model for CV mortality and hospitalisations for worsening heart failure [3]. This will provide estimates separately of the treatment effects for CV death and recurrent hospitalisation for heart failure, and of a weighted combination of these estimates with weights corresponding to the numbers of each

type of event. A similar approach will be taken using the using the method of Mao and Lin [4]. In the analyses of the composite primary endpoint, deaths and heart failure hospitalisations will be weighted by their frequency.

A primary COVID-19 analysis will be carried out on the primary endpoint and secondary time to event endpoints, in an attempt to minimise the impact of the COVID-19 pandemic. This will include all patients randomised until the end of March 2020 with a censoring date of 30 Sept 2020. This decision reflects the fact that IV iron administered prior to the initial lockdown would be expected to have effects persisting for at least six months. Additional sensitivity analysis will use time-varying treatment effects to investigate the impact of the COVID-19 pandemic on the results of the study for the primary endpoint (time to first and recurrent). Time will be divided into 5 periods; pre first lockdown in the UK, start of first lockdown until end of first lockdown, end of first lockdown until start of second lockdown, start of second lockdown until end of second lockdown, and end of second lockdown until end of defined patient follow-up. This will permit, in a descriptive fashion, the estimation of treatment effects in each period and the comparison of effects in lockdown and non-lockdown periods.

2.6.5 ADDITIONAL ANALYSES

The number of non-SAE blood transfusions and rates per 100 patient years will be summarised overall and by reason (trauma, surgery, haemorrhage and anaemia). The rates of transfusions will be compared between treatment arms using a negative binomial model adjusted for stratification variable and with log follow-up time as an offset. The rate ratio, 95% CI and p-value will be calculated.

The number and rate of non-SAE haemorrhages (per 100 patient years) will be summarised split by treatment arm, overall and by site (upper GI, lower GI, GI bleed, GU bleed, other bleed) and by severity (major, minor).

To help understand the mechanism of any potential benefit of IV iron on the described endpoints, we will compare (using a Wilcoxon rank sum test) haemoglobin, platelets, serum creatinine and eGFR between the randomised treatment groups at 4 months and 20 months, with all but platelets also assessed at the patient's last measurement.

The adjudications by the endpoints committee for non-fatal SAEs and causes of death will be summarised in the ITT population.

SBP, DBP, heart rate, weight and BMI and changes from baseline will be summarised over time. Mean levels and mean changes with associated 95% CIs will be plotted by study visit split be treatment group. The numbers and percentages with oedema and distribution of NYHA class will be summarised and plotted over time.

2.6.6 ASSUMPTION CHECKING

The proportional hazards/means assumption for the primary outcome will be tested informally by review of the cumulative incidence plots, and formally by adding a log(time)*treatment covariate in the relevant models and assessing its statistical significance at the 5% significance level. If the extent of any deviation from proportional hazards is

minor, the proportional hazards/means model results will be reported with a caveat that the hazard ratio represents approximately the average treatment effect over the follow-up period. If there is more extensive deviation, for instance clear evidence of the survival curves crossing, a further analysis will be stratified with appropriate time intervals.

2.7 SAFETY OUTCOMES

Safety outcomes post randomisation will be presented for the safety population, that is the randomised population excluding those in the IV iron arm where we have clear evidence that no study IV iron was received. Patients omitted from the safety analysis will have their serious adverse event (SAE) data listed.

2.7.1 ANALYSIS PERIODS

The safety analyses will be carried out in the Safety population for the following follow-up period:

- Within Study - end of study date (as noted in section 2.3) plus thirty days (withdrawal of consent subjects will not have thirty days added).

There will be no on-treatment reporting of safety events in this study, in part because you can only withdraw from one study arm. In addition, it is difficult to define the on-treatment period for this study, as treatment is only given when required and because the effect of the treatment is long lasting. We also note the concerns that have been expressed about on-treatment SAE analyses [5].

2.7.2 TIME TO EVENT SAFETY ENDPOINTS

The following safety endpoints, Within Study, will be analysed in the same way as the efficacy time to first event endpoints:

- Death due to infection
- Hospitalisation primarily for infection (first event)

2.7.3 TREATMENT EXPOSURE

In the IV iron arm, for each study visit, we will summarise the number of patients who could potentially have attended, the number attending remotely, the number attending face-to-face, the number infused with IV iron, and for those infused, summarise the doses infused. Summarise overall the distribution of the numbers of infusions received per patient and the total dose received.

2.7.4 SAES, DEATHS

SAEs will be summarised Within Study by treatment group, by system organ class and preferred term as classified by MedDRA (version 23.0). In addition, listings of SAEs will be produced for events considered severe, and in the IV iron arm for those considered to be at least possibly related to study drug and for those leading to permanent withdrawal from study drug. Additional tables will be produced for the system organ classes with 95% confidence

intervals (and p-values) for the differences in proportions and odds ratio for the proportions between the treatment groups, adjusted for stratification variables. Tables of preferred terms reported by more than 3% of the randomised population will also be produced. The total number of events, numbers of patients with first events, crude % of patients with events, rates of events /100 patient years of follow-up will be summarised by treatment group.

A listing of any SUSARs (serious unexpected serious adverse reactions) will be produced.

The distribution of the total number of SAEs will be reported for each category of outcome, action and severity (a listing will be provided if there are few events).

Adjudicated causes of death will be summarised by treatment group in the safety population.

A cumulative incidence plot Within Study split by treatment group will be produced for the time to first serious adverse event.

2.7.5 LABORATORY VALUES

Laboratory values and changes from baseline will be summarised in tables and plotted using box and whisker plots and using means and 95% CIs. Results may be transformed as appropriate.

Summaries will be provided, by treatment group, for the numbers and percentage of subjects with any post-baseline laboratory values of clinical concern:

- eGFR: < 30
- Hamoglobin: <11 (men)/<10 (women)
- MCV: <80 or >100
- MCHC: <30
- MCH: <26
- Platelets: <100
- Sodium: <135
- Potassium: <3.5 or >5.5
- Urea: >20
- CRP: >20

2.7.6 CONCOMITANT MEDICATIONS

The number and percentage of patients reporting use of common concomitant medications during the post-baseline period will be summarised by WHO (version Jan 2011) ATC levels 1 and 4.

3. TABLES AND FIGURES

Dummy reports will be produced and reviewed by the chief investigator. Approval of the content of the final statistical outputs will be documented prior to database lock.

4. LISTINGS

Listings of all derived datasets will be produced as excel spreadsheets. In addition, listings will be produced containing the information used for each output table and figure in the report.

Any listings required for a regulatory submission will be produced after database lock.

5. REFERENCES

1. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. J R Stat Soc B 2000; 62: 711-30.
2. Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. Biometrics 2000; 56: 554-62.
3. Y. Mazroui, S. Mathoulin-Pelissier, P. Soubeyranb and V. Rondeau (2012) General joint frailty model for recurrent event data with a dependent terminal event: Application to follicular lymphoma data. Statistics in Medicine, 31, 11-12, 1162-1176.4. Mao L, Lin DY. Semiparametric regression for the weighted composite endpoint of recurrent and terminal events. Biostatistics 2016; 17:390-403.
5. Yang F, Wittes J, Pitt B. Beware of on-treatment safety analyses. Clin Trials. 2019; 16 :63-70.

6. DOCUMENT HISTORY

This is the second version of the SAP. The following amendments were made (from version 1.0):

Section	Amendment
Cover page	New protocol version
1.6.3/1.6.4	Deviations and additional analyses now combined into one section (1.6.3). Details added for the reasoning for the deviations. Clarification that some of the subgroups were not specified in the protocol.
1.6.5	Renumbered to 1.6.4 due to above.
2.3	Clarification of disposition summaries.
2.5	Additional drug summaries added; urea added to the blood analyses (omitted in error in version 1.0).
2.6.3	Amendment to secondary endpoints (as documented in section 1.6.3). Clarification of missing data imputation analyses.
2.6.4	Minor wording changes to clarify COVID-19 analyses.
2.6.5	Minor wording changes to clarify additional analyses.
2.7.1	Clarification of 'within study'.
2.7.4	Removal of fatal SAE summary; clarification of analyses.
2.7.6	Clarification of drug summaries.

Clinical Endpoint Committee Charter and Operating Manual

Charter Version No:	2.0
Study Title:	Effectiveness of intravenous iron treatment vs standard care in patients with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRONMAN)
Short Title:	IRONMAN
Chief Investigator:	Dr Paul Kalra
CEC Chair:	Professor John Cleland
Sponsor:	NHS Greater Glasgow & Clyde and the University of Glasgow
Sponsor Ref:	GN15CA190

Contents

1. Background

IRONMAN is a randomised trial comparing the effects on morbidity and mortality of administering, or not, IV iron, repeated as required at regular intervals, to patients receiving guideline-recommended treatments for heart failure with a reduced left ventricular ejection fraction who have evidence of iron deficiency.

IRONMAN will utilise a PROBE (prospective, randomised open-label, blinded endpoint) design. Robust blinding of the administration of IV iron is difficult and complex and would impair recruitment and markedly increase expense. However, Clinical Event Committee (CEC) review and adjudication of potential study endpoint events will be blinded.

Adjudication ensures that events critical to the analysis of study results are assessed in a uniform manner, eliminating the variability associated with site-based event evaluation. This facilitates reliable pooling of data within a trial and improves the validity of comparisons with published data.

2. Purpose

This Charter provides a framework for evaluation but should be considered a living document that will evolve during the adjudication process should decisions have to be made for unforeseen circumstances or with sparse data.

All hospitalisations and deaths will be reviewed by the CEC in order to categorise potential endpoint events.

3. Composition of the Clinical Endpoint Committee (CEC)

CEC Member	Affiliation	Contact Details
Professor John Cleland (Chair)	Glasgow Clinical Trials Unit	John.Cleland@glasgow.ac.uk
Dr Pierpaolo Pellicori	Glasgow Clinical Trials Unit	Pierpaolo.Pellicori@glasgow.ac.uk
Dr Fraser Graham	Glasgow Clinical Trials Unit	Fraser.Graham@glasgow.ac.uk

In the event that a CEC member is unable to continue participation, the CEC Chair will recommend a replacement to the Steering Committee. The Steering Committee has the final decision as to the replacement.

All members of the CEC will have documented training in Good Clinical Practice and the study-specific electronic endpoint adjudication system.

4. Roles and Responsibilities

The role of the CEC in IRONMAN is:

- To provide independent and unbiased review of clinical endpoint events which occur during the trial
- To ensure unified and unambiguous events evaluation practices across the trial, through application of standardised event criteria, as outlined in this Charter
- To compensate for regional diversity in medical practice for event evaluation and classification, thereby reducing the impact of this diversity.

4.1 CEC Chair

The CEC Chair will be responsible for:

- Acting as the primary liaison between the CEC and the Steering Committee
- Proposal of CEC members
- The overall conduct of the CEC
- Developing the CEC Charter in liaison with the Steering Committee and the study sponsor
- Ensuring that all adjudicators perform the tasks as determined in this Charter and in accordance with the protocol
- Undertaking the CEC member responsibilities detailed below.

4.2 CEC Members

CEC members will be responsible for:

- Reading and understanding the content of the CEC Charter
- Reviewing the relevant de-identified clinical data about a subject identified as having experienced a suspected event of interest requiring adjudication
- Adjudicating pre-specified clinical events of interest in keeping with the study definitions outlined in this Charter
- Timely submission of adjudication decisions
- Communicating with the CEC Chair about needs when necessary
- Attending scheduled CEC meetings throughout the study.

4.3 RCB Endpoint Office

The CEC will be supported by the Endpoint (EP) Office within the Robertson Centre for Biostatistics (RCB), University of Glasgow. The EP Office will:

- Interact with the CEC as appropriate
- Procure and process death certificates for all fatal events
- Review event documentation uploaded by the study sites to confirm that the evidence required to support endpoint adjudication has been submitted and that information that might compromise patient privacy or assigned therapy has been redacted
- Liaise with study sites in support of the adjudication process
- Prepare study-specific user guidance in the endpoint adjudication system and related processes for use by the CEC and study sites
- Coordinate and attend CEC meetings, inputting Phase 2 adjudication decisions (see 8.2) to the study web portal at direct instruction of the CEC.

5. Clinical Events to be Reviewed

The primary and secondary efficacy and safety endpoints in the IRONMAN trial are shown below. Events requiring adjudication are shown in bold. <u>As recurrent events analyses are proposed, all events must be adjudicated and not only the first event.</u> The primary endpoint is CV mortality or hospitalisation for worsening heart failure (analysis will include first and recurrent hospitalisations).

Secondary efficacy endpoints include:

1. **Cardiovascular mortality**
2. **Hospitalisation for worsening heart failure**

3. All-cause mortality
4. **CV mortality or first hospitalisation for major CV event (stroke, MI, heart failure)**
5. Physical domain of QoL
6. Overall QoL assessment
7. Combined all-cause mortality or first all-cause unplanned hospitalisation
8. Days dead or hospitalised at 2.5 years (minimum duration of follow-up)
9. Quality-adjusted days alive and out of hospital at 2.5 years
10. **CV hospitalisation**
11. **All-cause hospitalisation**

Secondary safety endpoints include:

1. **Death due to infection**
2. **Hospitalisation primarily for infection**

6. Identification of Potential Endpoints

The IRONMAN study will use electronic data capture. The identification of potential endpoints, uploading of source documents, review and collation of endpoint information and CEC review and classification of potential endpoints will be facilitated by the IRONMAN web portal.

The Principal Investigator (PI) at each site will review and classify all Serious Adverse Events (SAE) reports. The EP Office will prepare potential endpoint events, i.e. all hospitalisations and deaths, for further review by the CEC.

Site teams will upload the required source data for all events identified as potential clinical endpoints.

Data sources include SAE reports, discharge summaries or letters, death certificates, PI SAE review for hospitalisations and deaths and electronic records obtained by linkage to national datasets for hospital admissions and deaths.

The CEC will base its decision on the investigator report but may seek clarification or further information before the making a final decision. All differences between the PI and CEC adjudication will be recorded so that a clear decision trail exists.

7. Endpoint Definitions

Deaths

All-cause mortality does not require adjudication, however deaths due to CV causes or infection do. Other causes and modes of death are also of scientific interest. Four sources of information will be considered:

1. Death certificates, showing the place and primary and secondary causes of death. Note: Where the place of death is listed as an address other than a hospital, the Endpoint Office will redact the address and, where possible, add a note to the PDF copy of the certificate to indicate whether the place was a private address or a care home.
2. Hospital discharge summaries or data obtained via record linkage or from SAE reports showing the pattern of events and diagnoses preceding death

3. A brief narrative from the investigator
4. Completed ‘death’ information sourced from SAE data.

The provisional cause of death will be that indicated by the investigator. The CEC will act as an oversight review panel to ensure that the information is coherent and credible and to seek clarifications where appropriate. The CEC will also ensure that contributory causes of death are recorded in addition to the primary cause.

The final cause of death will be adjudicated only once information from all four of the above sources is available unless it is clear that the information does not exist or will not be available for CEC review.

At the end of the study, the CEC will re-review all deaths and will take into account previous events preceding death to form a narrative that allows death to be reviewed in terms of place, mode and cause.

Hospitalisations

All-cause hospitalisation does not require adjudication, however those due to CV causes or infection do. Other causes for hospitalisation are also of scientific interest.

Three sources of information will be considered:

1. Hospital discharge summaries or data obtained by record linkage to national databases
2. A brief narrative from the investigator
3. Completed ‘hospitalisation’ information sourced from SAE data.

The provisional cause of hospitalisation will be that indicated by the investigator. The CEC will act as an oversight review panel to ensure that the information is coherent and credible and to seek clarifications where appropriate. The CEC will also ensure that contributory causes for hospitalisation are recorded in addition to the primary cause.

Definitions

7.1 Death will be adjudicated as:

7.1.1 Cardiovascular death, which includes nine sub-categories:

1. Acute coronary syndrome (ACS) / myocardial infarction (MI) – Such deaths will usually be in hospital soon after admission for an ACS documented by appropriate investigation. Deaths occurring some days after an ACS should be classified as sudden or due to heart failure.

2. Sudden cardiac death – Defined as a sudden event, probably due to an arrhythmia. To be considered a sudden cardiac death, the adjudicator should believe that the life of the patient might have been prolonged life by six months or more if the patient had an implanted defibrillator or had been successfully resuscitated. As a consequence, a patient with end-stage heart failure might die suddenly but should, nonetheless, be adjudicated as a heart failure death. Patients who are resuscitated from sudden death who subsequently die before hospital discharge will be considered sudden deaths.

3. Heart failure death – Patients dying of progressive worsening or heart failure or who die suddenly in the context of recurrent heart failure admissions.

4. Cardio-renal death - Where death is primarily related to renal failure as a consequence of cardiac dysfunction. Many or all of these patients might be classified as heart failure deaths but this category provides greater clarity. Death related to hyperkalaemia is also included in this category since it usually reflects the effect of CV therapy in patients with heart failure and renal dysfunction. However, if the patient dies of renal failure or hyperkalaemia unrelated to cardiac dysfunction or CV therapy, this should not be classified as CV. The operational criteria for adjudicating death as cardio-renal death are (non-inclusive):
    - Hyperkalaemia thought to be related to cardiac medications
    - Acute or sub-acute worsening renal function with lowest eGFR<15ml/min.

5. Stroke death – Where it leads directly or indirectly (e.g. - due to pneumonia) to death.

6. Haemorrhagic death (unless related to sufficient accidental trauma or violence that the patient would be expected to die even if they had not been on anti-coagulants - a cardiovascular therapy) - Most haemorrhage, gastro-intestinal or other, in patients with CV disease could be related to anti-thrombotic therapy. Any large loss of blood from the circulation could be considered a CV event.

7. Death due to treatments for cardiovascular disease including drugs, procedures or devices

8. Death due to pulmonary embolism

9. Other cardiovascular death

7.1.2 Non-cardiovascular death, which includes six sub-categories:

1. Cancer - Importantly, severe infections leading to death in the context of cancer during the treatment phase will be coded as cancer-related death.

2. Respiratory - Death due to chronic lung disease, lobar pneumonia or bronchopneumonia should be regarded as respiratory deaths. Although death might also be classified as due to infection, death due to respiratory infection should be recorded here. Importantly, when the acute respiratory distress is thought to be related to heart failure itself, it will be recorded as a heart failure death.

3. Renal - This category will apply to acute or chronic renal failure that was not recorded as cardio-renal death. Death due to urinary infection should be attributed to infection.
4. Trauma and non-cardiovascular procedures - This category includes death due to suicide, violence or accidents, including falls leading to fractures and death. Deaths due to non-cardiovascular medical procedures and surgery will be included here.

5. Infection - This category includes septicaemia, often with multi-organ failure. Urinary infection is likely to be a major contributor. Respiratory infection should be included under respiratory.

6. Other

7.1.3 Undetermined cause of death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause.

Inability to classify the cause of death may be due to lack of information (e.g., the only available information is 'patient died') or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death should therefore be discouraged and apply to few patients.

The adjudicator will record both the primary cause and contributory causes of death. This strategy will make classification easier, for instance for deaths with complex cardio-renal and heart failure causes. Each death may have only one primary cause but could have several contributory causes.

Investigators will also be asked to state whether the death was sudden or unexpected. An expected death is one where the patient has a protracted period of ill-health associated with very poor quality of life where death may be considered a welcome release. An unexpected death is one where the patient had at least a moderate quality of life prior to death, even if they had very poor cardiac function, who died as a result of trauma, a planned medical intervention or a sudden vascular or arrhythmic event or who was simply 'found' dead.

7.2 Hospitalisation

Hospitalisation will be adjudicated as cardiovascular and non-cardiovascular using the same classification criteria as for death, except that the sudden death category will be re-labelled as arrhythmia with a sub-classification of ventricular and supra-ventricular.

A hospitalisation will only be confirmed as an endpoint where, in addition to fulfilling the required criteria, the hospitalisation period results in **two** date changes (i.e. lasts >24 hours) unless death occurs during admission.

Acute Coronary Syndrome (Myocardial Infarction) and Stroke
Only events leading to hospital admission or reported by a specialist will be considered. Diagnoses should be supported by relevant investigations. Stroke events include any neurological deficit thought to be due to a vascular event provided it lasts >12 hours, even if there is a full recovery.

Heart Failure (HF) related hospitalisation, including any associated with a substantial intensification of treatment for heart failure, should be classified as:

1. Primary cause, where HF is the dominant reason for admission with or without an precipitating factor (precipitating factors should be recorded as contributory causes)
2. Contributory cause, where HF is not the dominant reason for admission but contributory
3. Late complication, where HF did not contribute to admission but complicated the post-admission period.

Only the first two categories will contribute to the primary endpoint.

The use of intravenous therapies, mechanical circulatory support or mechanical fluid removal (e.g. ultrafiltration, hemofiltration or dialysis) and the results of relevant diagnostic tests should be considered during CEC review.

Example:
A doctor reports that a patient was admitted for an acute coronary syndrome and developed pulmonary oedema three days later, confirmed radiologically and treated with 80mg of furosemide given intravenously. So, this is a HF-related hospitalisation (late complication). However, this would not be classified as a primary HF hospitalisation and would NOT count towards the primary endpoint.

8. Review of Potential Endpoints

CEC review of potential endpoints will be facilitated by the IRONMAN study web portal. Adjudicators will be able to view the eCRF pages and documents relating to the event and complete an adjudication screen. Adjudicators will also be able to request additional information if required. CEC members will be trained in the review process by the EP Office.

An electronic adjudication folder will be prepared for each potential endpoint event and will be available for CEC review via the trial web portal. The folder will contain:

- Screening CRF forms completed by site:
  - Medications
  - Heart failure history
  - Cardiovascular history
  - Clinical and functional assessment
  - Investigations
  - Screening blood tests
- SAE report
- PI SAE review forms
- Source documents, e.g. discharge summaries and/or death certificates
- Record linkage information where applicable.

8.1 Phase 1 CEC review

Each potential endpoint package will be reviewed by one CEC member. The CEC member will be encouraged to bring any equivocal cases to a CEC meeting for joint adjudication.

In order to maintain the blinded nature of the CEC review process, any CEC member with a clinical role at an IRONMAN study site will be excluded from reviewing and classifying potential endpoint events affecting participants at that site. The CEC member's web portal access will be restricted to exclude access to any potential endpoint data from that site.

On receipt of an email notification advising that potential endpoints are available for Phase 1 review, the CEC member will:

- Log in to the IRONMAN web portal and select 'Endpoints'
- Select a potential endpoint for review
- Review the details of the event by accessing the eCRF forms and supporting documentation
- Adjudicate the event according to the EP definitions as detailed in this charter by either:

- Accepting the outcome of the PI review
- Assigning alternative primary and contributory (if applicable) causes for the event.
- Confirming that the event is 'not an endpoint,' i.e. it does not fulfil any of the Endpoint Definitions as detailed in this Charter

- Forward the event for Phase 2 review
- Request additional information before a classification decision is made.
  Details of the information required should be added to the Additional Information textbox on the EP review page. An automatic email notification will be forwarded to the site (copied to the EP Office) advising that additional information is required. When the requested information becomes available, it will be reviewed by the EP Office and re-submitted to the adjudicator. In instances where it is confirmed that efforts to obtain the requested information have been unsuccessful (e.g. because the study site has indicated that the information is not available), the event should be forwarded by the Phase 1 reviewer for Phase 2 review at a scheduled CEC meeting.

8.2 Phase 2 CEC Review

The CEC will convene at regular intervals throughout the study, as required. In general, these will be face-to-face meetings, however, if this is not possible, a meeting by teleconference or videoconference may substitute.

The frequency of meetings will depend on the quantity of events requiring Phase 2 review by the CEC. A meeting may be cancelled if there is no business for discussion or cases for review by the full Committee.

The primary objective of CEC meetings is the 'Phase 2 review' and classification of those events for which a final classification decision has not been achieved by the Phase 1 review process outlined above.

Events may also be submitted directly by the EP Office for Phase 2 review, e.g. where > one SAE report has been submitted for one hospitalisation period.

Phase 2 review of an event constitutes the discussion and adjudication of the event by the CEC as a group. The EP Office will coordinate and attend Phase 2 meetings and will input Phase 2 adjudication decisions to the study web portal at direct instruction of the CEC.

Should the CEC be unable to arrive at a classification verdict for an event due to incomplete or inadequate information and it is felt that such information should be obtainable (i.e. the study site has not indicated that the information required is unavailable), the CEC Chair will detail the precise information/documentation that is needed to achieve classification and this will be requested from the site. Adjudication of the event will be deferred until a subsequent CEC meeting when the requested information has been made available (or, when, despite best efforts, it is confirmed that the information will not be obtainable).

Once adjudication is completed at either Phase 1 or Phase 2, an automatic email notification will be forwarded to the EP Office advising that an event has been adjudicated.

Additional guidance for the CEC endpoint review and adjudication process using the IRONMAN web portal is provided in the IRONMAN Clinical Endpoint Committee Adjudication User Guidance.

8.3 Adjudication Timelines

The CEC members will make every effort to review events and to enter their adjudication decisions to the study web portal within 2 to 4 weeks from notification that the events are available for Phase 1 review.

To facilitate the prompt adjudication of events, it is expected that event data received by the CEC will be as clean and complete as possible and that any CEC queries or requests are resolved in a timely fashion.

9. Referenced Documents

IRONMAN Clinical Endpoint Committee Adjudication User Guidance

10. CEC Charter Version History

Version	Details	Date
1.0	Initial creation	24/04/2018
2.0	• CEC membership details finalised • References to CEC Coordinator replaced with RCB EP Office with additions to EP Office role • The term 'sepsis' replaced with 'infection' • Removal of option for an event to be classified as 'probable' where supporting evidence is inconclusive • Deletion of information documented elsewhere, e.g. in SAP • Additional detail of information available to CEC via web portal • Clarification of the phases of the review process via web portal • Documentation of restriction of web portal access to maintain blinded review process where a CEC member has a delegated clinical role at an IRONMAN study site • Addition of option for EP Office to submit events directly for Phase 2 review • Addition of option for the CEC to classify an event as 'not an endpoint' following Phase 1 review • Removal of QC process • Addition of reference to IRONMAN Clinical Endpoint Committee Adjudication User Guidance • Formatting and grammatical changes • Charter moved to new template (Form 26.001A, v2.0)	04/02/2021

11. Approvals

The following CEC and Sponsor representatives have approved this Charter:

Name	Role	Signature	Date
Dr Paul Kalra	Chief Investigator		
Professor Ian Ford	Study Director		
Professor John Cleland	CEC Chair		
Dr Pierpaolo Pellicori	CEC Member		
Dr Fraser Graham	CEC Member		
Dr Maureen Travers	Sponsor Representative		