Clinical trial results:
INtravenous Iron to Treat Anaemia in CriTical Care Survivors (INTACT): a feasibility study

Summary

EudraCT number	2018-000767-91
Trial protocol	GB
Global end of trial date	16 March 2020

Results information

Result version number	v1 (current)
This version publication date	06 May 2021
First version publication date	06 May 2021
Summary attachment (see zip file)	Manuscript draft (INTACT_ManuscriptDraftPDF.pdf)

Trial information

Trial identification

Sponsor protocol code	PID13493

Additional study identifiers

ISRCTN number	ISRCTN13721808
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1209-6873

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	University Offices, Wellington Square, Oxford, United Kingdom, OX1 2JD
Public contact	Akshay Shah, University of Oxford, +44 1865387906, akshay.shah@ndcls.ox.ac.uk
Scientific contact	Akshay Shah, University of Oxford, +44 1865387906, akshay.shah@ndcls.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a feasibility study aiming to find out whether it is possible to give intravenous (through a drip) iron to patients with anaemia (low blood count) who have survived intensive care (ICU). A feasibility study is a short trial with a small number of people taking part, to help us decide how a larger study would work. Important questions that we are asking in this feasibility study are
(i) How easy is it to recruit participants?
(ii) How easy is it to collect the relevant information we would need for a future large trial?

Our ultimate aim is to complete a larger trial which will test whether or not intravenous iron will treat anaemia in ICU survivors and improve quality of life after discharge from hospital. This would require external funding and be a separate ethics application.

Protection of trial subjects:

The trial had two committees:
(1) Trial Management Group (TMG)
The TMG will be responsible for the day to day running and management of the trial. A core team consisting of the CI and up to three other investigators will aim to meet at least two weekly during the planning stages of the trial and with the wider team less frequently when the trial is running.

(2) Trial Oversight Group (TOG)
The TOG will include independent clinicians experienced in the fields of clinical trials, intensive care and haematology along with an independent statistician. The TOG will work closely with the TMG and will provide overall supervision of the trial through its independent chair.
The TOG responsibilities will include:
- Provide overall supervision of the trial and to ensure it is being conducted in accordance with Good Clinical Practice
- Advise on protocol development and ensure adherence to the protocol during the trial period.
- Establish frequency of meetings prior to commencement of trial
- Provide advice to the CI and TMG through its independent chair and funding body, if appropriate, on all aspects of the trial
- Review AE and SAEs reported by the CI
- Monitor safety of study participants and to suggest any amendments to the protocol or termination of the trial if deemed necessary for patient safety

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 98

Worldwide total number of subjects	98
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	46
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled from four ICUs across three centres (Oxford University Hospitals NHS Foundation Trust, Royal
Infirmary of Edinburgh NHS Lothian, Royal Berkshire Hospital NHS Foundation Trust) from 17th September 2019 to 20th December 2020 with final patient follow-up completed on 13th March 2020.

Pre-assignment

Screening details:

A total of 606 patients were screened, and of the 290 (48%) that were eligible for recruitment, 98 (34%) were randomised over 15 months.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label study

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention (Iv iron) arm

Arm description:

Participants randomised to the IV iron group received, in addition to usual care, a single dose of 1000mg of ferric
carboxymaltose diluted in 100mls of 0.9% saline as an infusion over 15 minutes.

Arm type	Experimental
Investigational medicinal product name	Ferric carboxymaltose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants randomised to the IV iron group received, in addition to usual care, a single dose of 1000mg of ferric
carboxymaltose diluted in 100mls of 0.9% saline as an infusion over 15 minutes.

Arm title	Comparator

Arm description:

Usual medical care consisting of monitoring and red blood cell transfusion if required

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Intervention (Iv iron) arm	Comparator
Started	49	49
Completed	47	49
Not completed	2	0
Consent withdrawn by subject	1	-
Lost to follow-up	1	-

Baseline characteristics

End points

End points reporting groups

Reporting group title	Intervention (Iv iron) arm

Reporting group description:

Participants randomised to the IV iron group received, in addition to usual care, a single dose of 1000mg of ferric carboxymaltose diluted in 100mls of 0.9% saline as an infusion over 15 minutes.

Reporting group title	Comparator

Reporting group description:

Usual medical care consisting of monitoring and red blood cell transfusion if required

Subject analysis set title	Primary feasibility outcomes
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Recruitment rate was calculated by the number of participants randomised as a proportion of the total number of eligible patients. The protocol adherence rate was calculated as the number of participants allocated to the intervention who received the study drug over the number of participants allocated to the intervention. HRQoL questionnaire completion rates were calculated as the number completed at each time point over the number expected (total randomised less those participants who died). Rates, together with 95% confidence intervals (CIs) were estimated based on data collected are reported.

Subject analysis set title	Secondary outcomes
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Secondary outcomes included the following clinical, laboratory and HRQoL outcomes: (i) incidence of new nosocomial infection; (ii) in-hospital mortality; (iii) hospital LOS; (iv) changes in Hb, iron profiles, hepcidin and routine biochemistry from blood samples collected at baseline, 28 and 90 days post-randomisation; (v) HRQoL measured by Multidimensional Fatigue Inventory-20 (MFI-20), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and EuroQoL-5D-5L (EQ-5D-5L) questionnaires collected at baseline (pre-randomisation), and 28 and 90 days post-randomisation; and (vi) healthcare resource use, including hospital readmissions.

Primary: Recruitment rate

End point title	Recruitment rate

End point description:

Between September 2018 and December 2019, 290 (48%) of 606 patients approached were eligible to consent to participate. The overall recruitment rate for the trial was 34% (95% CI 28% to 40%). Overall, 98 patients were recruited from 3 sites over 15 months, a rate of 6.5 per month meeting the amber category for the stop-go criteria in the trial (Table 11).

End point type	Primary

End point timeframe:

September 2018 to December 2019.

End point values	Intervention (Iv iron) arm	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: Percentage	49	49		

Statistical analyses

Statistical analysis title	Recruitment and randomisation rate
Statistical analysis description:	
Recruitment rate was calculated by the number of participants randomised as a proportion of the total number of eligible patients.	
Comparison groups	Intervention (Iv iron) arm v Comparator
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	Chi-squared
Parameter estimate	95% CI
Confidence interval	
level	95 %
sides	2-sided
lower limit	28
upper limit	40

Notes:

[1] - Feasibility outcome

Primary: Protocol adherence	
End point title	Protocol adherence
End point description:	
Of the 49 participants randomised to receive IV iron, 47 received it (96%, 95% CI 86% to 100%). One participant died and one participant withdrew before IV iron was administered.	
End point type	Primary
End point timeframe:	
September 2018 to December 2019	

End point values	Intervention (Iv iron) arm	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: Percentage	47	49		

Statistical analyses

Statistical analysis title	Protocol adherence

Statistical analysis description:

Of the 49 participants randomised to receive IV iron, 47 received it (96%, 95% CI 86% to 100%). One participant died and one participant withdrew before IV iron was administered.

Comparison groups	Intervention (Iv iron) arm v Comparator
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.05
Method	Chi-squared
Parameter estimate	95% Confidence interval
Confidence interval	
level	95 %
sides	2-sided
lower limit	86
upper limit	100

Notes:

[2] - Feasibility outcome

Primary: Follow-up rate

End point title	Follow-up rate

End point description:

All HRQoL outcomes were collected for at least 80% of survivors at 90 days.

End point type	Primary

End point timeframe:

September 2018 to March 2020

End point values	Intervention (Iv iron) arm	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: Percentage	49	49		

Statistical analyses

Statistical analysis title	Follow-up rates

Statistical analysis description:

HRQoL questionnaire completion rates were calculated as the number completed at each time point over the number expected (total randomised less those participants who died).

Comparison groups	Intervention (Iv iron) arm v Comparator

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.05
Method	Chi-squared
Parameter estimate	95% Confidence interval
Confidence interval	

Notes:

[3] - Feasibility outcome

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Overall trial period

Adverse event reporting additional description:

The following rare events, if serious, must be reported on the trial specific SAE form:
Anaphylactic/anaphylactoid reactions
Loss of consciousness / syncope
Bronchospasm
Angioedema and facial oedema
Severe anaemia (Hb <80 g.l-1) at 28 and/or 90-day post randomisation follow-up

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Intervention (IV iron) group
Reporting group description: -	
Reporting group title	Comparator (usual care) group
Reporting group description: -	

Serious adverse events	Intervention (IV iron) group	Comparator (usual care) group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Intervention (IV iron) group	Comparator (usual care) group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No pre-defined SAEs or non-SAEs occurred during the course of the trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Our trial has limitations. It was open label, which may have introduced performance bias, particularly for HRQoL
measures, and attrition bias. Ferric carboxymaltose is a challenging and costly substance to blind due to its rusty brown
colour.

Notes: