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Intravenous iron to treat anaemia following critical care (INTACT): a feasibility randomised controlled trial

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Abstract:	Background: To determine if intravenous iron is a feasible treatment option for patients being discharged from the intensive care unit (ICU) with moderate and severe anaemia (haemoglobin ≤100 g/L). Methods : An open-label, multicentre, feasibility randomised controlled trial (RCT) with 1:1 randomisation to either intravenous iron or usual medical care. Primary feasibility outcomes included recruitment rates, protocol adherence and completeness of follow-up at 28 and 90 days post-randomisation. Results : Ninety-eight participants were randomised over 15 months (49 in each arm) across four ICUs. The overall recruitment rate was 34% with 6.5 patients recruited on average per month. Forty-seven out of 49 (96%) participants received the intervention. All health-related quality of life (HRQoL) measures were collected for 79/93 (85%) survivors at 90 days. Mean (SD) haemoglobin was higher in the intravenous iron group at 28 days (119.7 (13.3) vs. 106.7 (14.9)) and 90 days (130.5 (15.1) vs. 122.7 (17.3), adjusted mean difference 11.0 (95% CI: 5.0, 17.0) g/L, p <0.001). There were no differences in infection, mortality and HRQoL scores. The median (IQR) post-ICU hospital stay was shorter in the intravenous iron group, but this was not statistically significant (5.0 (3.0 to 13.0) vs. 9.0 (5.0 to 16.0) days, p=0.15). Hospital readmissions in the first 90 days following ICU discharge were lower in the intravenous iron group (7/40 (17.5%) vs. 15/39 (38.5%), p = 0.037). Conclusion : A large RCT of intravenous iron to treat anaemia in ICU survivors is feasible. Patient-centred outcomes pointed towards benefit but our trial was not powered to show such differences.
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Intravenous iron to treat anaemia following critical care (INTACT): a feasibility randomised controlled trial

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Abstract

Background: To determine if intravenous iron is a feasible treatment option for patients being discharged from the intensive care unit (ICU) with moderate and severe anaemia (haemoglobin ≤100 g/L).

Methods: An open-label, multicentre, feasibility randomised controlled trial (RCT) with 1:1 randomisation to either intravenous iron or usual medical care. Primary feasibility outcomes included recruitment rates, protocol adherence and completeness of follow-up at 28 and 90 days post-randomisation.

Results: Ninety-eight participants were randomised over 15 months (49 in each arm) across four ICUs. The overall recruitment rate was 34% with 6.5 patients recruited on average per month. Forty-seven out of 49 (96%) participants received the intervention. All health-related quality of life (HRQoL) measures were collected for 79/93 (85%) survivors at 90 days. Mean (SD) haemoglobin was higher in the intravenous iron group at 28 days (119.7 (13.3) vs. 106.7 (14.9)) and 90 days (130.5 (15.1) vs. 122.7 (17.3), adjusted mean difference 11.0 (95% CI: 5.0, 17.0) g/L, p <0.001). There were no differences in infection, mortality and HRQoL scores. The median (IQR) post-ICU hospital stay was shorter in the intravenous iron group, but this was not statistically significant (5.0 (3.0 to 13.0) vs. 9.0 (5.0 to 16.0) days, p=0.15). Hospital readmissions in the first 90 days following ICU discharge were lower in the intravenous iron group (7/40 (17.5%) vs. 15/39 (38.5%), p = 0.037).

Conclusion: A large RCT of intravenous iron to treat anaemia in ICU survivors is feasible. Patient-centred outcomes pointed towards benefit but our trial was not powered to show such differences.

The trial was prospectively registered at www.isrctn.com as ISRCTN16403302.

Key words: Anaemia; critical care; intravenous iron; outcomes

Take home message

This RCT demonstrates the feasibility and safety of intravenous iron for treating moderate and severe anaemia ICU survivors, with evidence of biological efficacy and potential improvements in clinical outcomes.

A large trial is needed to confirm these findings.

Introduction

Anaemia is a well-recognised complication of critical illness and approximately 70-80% of intensive care unit (ICU) survivors are anaemic at hospital discharge [1, 2]. ICU patients display the hallmarks of anaemia of inflammation (AI), which is characterised by systemic hypoferraemia, bone marrow reprogramming, and decreased erythrocyte lifespan [3, 4]. Post-ICU anaemia can persist for up to one year following ICU discharge [1, 5, 6] and is associated with increased mortality, poor physical recovery and high levels of fatigue in ICU survivors [5, 7, 8]. Fatigue, the cardinal symptom of untreated anaemia, has been reported to be one of the most distressing symptoms in ICU survivors [9].

Intravenous (IV) iron is a biologically plausible treatment for AI in ICU patients but there are uncertainties about clinical efficacy and safety, including infection [10-12]. Data from a small number of randomised controlled trials (RCTs) have demonstrated a modest effect on haemoglobin (Hb), particularly in the post-ICU period [13, 14]. In these trials, iron was administered early in an ICU admission during the period of greatest physiological stress, heightened inflammation and when erythropoiesis is profoundly impaired [15]. Experimental work has demonstrated that iron therapy may be more efficacious after the acute phase of inflammation [16]. There is also growing interest in the potential role of the key iron regulatory hormone – hepcidin, as it may be a more reliable marker of iron status than current tests such as ferritin which are confounded by inflammation [17].

We hypothesised that treating anaemia when patients are *recovering* from critical illness may be a more appropriate time point for intervention. This may allow for a better assessment of the therapeutic window of IV iron on patient-centred outcomes. To inform the design of a future, adequately powered trial, we conducted a feasibility RCT of IV iron in patients being discharged from ICU with moderate and severe anaemia (Hb ≤100 g/L) to: (i) address rates of recruitment and follow-up; (ii) Hb recovery profiles in the post-ICU period; and (iii) variance of possible outcome measures for a future trial. Our research is aligned with recommendations from guidelines that have called for research into the optimal use of iron therapy in ICU patients (18).

Methods

This report was prepared according to the CONSORT Extension to Pilot and Feasibility Trials guidelines [19].

Trial design and oversight

INTACT was an investigator-initiated, multicentre, open-label, feasibility, parallel group RCT with 1:1 randomisation conducted across four ICUs of three United Kingdom (UK) National Health Service (NHS) centres. The trial protocol was registered prospectively on the ISRCTN registry (ISRCTN13721808), approved by the NHS South Central - Berkshire B Research Ethics Committee (18/SC/0308), and published previously [20]. The trial was overseen by an independent trial oversight group and managed by the Oxford Clinical Trials Research Unit (OCTRU).

Participants

Patients were eligible to participate if they required an ICU/ high-dependency unit stay for at least 24 hours, were deemed clinically stable for step-down to a general ward by the attending physician and the last measured laboratory Hb was ≤100 g/L. Exclusion criteria included active uncontrolled infection, severe chronic liver disease or personal or family history of iron overload disorders. A complete list of eligibility criteria and details of protocol amendments are provided in **Supplementary Tables 1, 2 and 3**.

Randomisation

Participants were randomised on a 1:1 basis to receive either IV iron (ferric carboxymaltose) or usual care using minimisation on a secure web-based system controlled by OCTRU, stratified on anaemia severity (Hb <80 g/L vs. 80-100 g/L) and participant ICU length of stay (LOS) (<7 days vs. ≥7 days).

Study procedures

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. This could be administered at any point between randomisation and hospital discharge. The iron formulation was chosen on the basis of a low side-effect profile, ease of administration and evidence of efficacy in other patient populations [21, 22].

Usual care consisted of routine ward-based care including observation with monitoring and blood transfusion when required according to current UK guidelines [23]. It is not routine practice to administer IV iron in patients discharged from ICU. Therefore, any decision to do so was at the discretion of the treating clinician, independent of the study, and recorded in the study case report forms.

Details of data collection and management are available in our published protocol [20]. Participants were followed up at 28 and 90 days post-randomisation. In order to maximise study retention, we employed a multimodal strategy of invitation to weekly ICU follow-up clinics, home visits by a member of the research team and telephone-only follow-up for participants who lived outside a reasonable geographical area.

Outcomes

The primary feasibility outcomes included (i) recruitment and randomisation rates (overall and by centre); (ii) protocol adherence to the study drug schedule; and (iii) completion of health-related quality of life questionnaires (HRQoL) at 90 days post-randomisation.

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. The FACIT-F tool [24] has been validated to assess fatigue in ICU survivors [25]. Infection was defined as 'commencement of new antibiotic therapy or escalation from prophylactic antibiotics for a confirmed or strongly suspected new infection'. A traffic light 'stop-amend-go' system was established *a priori* to guide decision making for a definitive trial (**Supplementary Table 4**) [26].

Laboratory measurements

Study-specific blood samples were collected at baseline, 28 and 90 days post-randomisation. Measurements obtained from local laboratories included Hb, urea & electrolytes, liver function tests, serum phosphate, C-reactive protein (CRP), 'iron profile' (serum ferritin, serum iron, transferrin saturation (Tsat)), erythropoietin (EPO) and vitamin D. A small volume of serum (600 μL) was aliquoted and reserved for measurement of serum hepcidin and soluble transferrin receptor (sTfR). These were assayed at a central laboratory by enzyme-linked immunoassay. Further details can be found in **Supplementary Table 5**.

Statistical analysis

No formal sample size calculation was undertaken but we planned to enrol up to 130 participants in order to provide enough data to inform the design of a future, statistically powered, multicentre RCT.

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.

Baseline data are described as proportions for categorical variables, and as mean (standard deviation (SD)) or median (interquartile range (IQR)) for continuous variables depending on the distribution. All clinical, HRQoL and laboratory outcomes were analysed on an intention-to-treat basis and no missing data were imputed. For categorical variables outcomes, a risk ratio (RR) and corresponding 95% CI was calculated and a Chi-squared test was utilised to compare the treatment groups or a Fisher's exact test if numbers were lower than 5 in any group. Data distributions for continuous variables were inspected and the assumption of equal variances assessed using Levene's test and where met, an independent sample t-test was used. Where there was evidence of skew or low numbers in each group, a Mann-Whitney rank test was used instead.

A multilevel mixed-effects model was used to generate estimates of the repeated key secondary HRQoL and laboratory outcomes at 28 and 90 days post-randomisation with a random intercept for participants and independent variance structure. The model included robust standard errors based on hospitals as clusters, a time by treatment interaction with time as a categorical variable and was adjusted for the baseline values of the outcome (if appropriate) and stratification factors. All analyses were undertaken using Stata version 15.1 (STATACorp LP, www.stata.com). Treatment estimates, 95% CIs and p-values are reported with significance declared at $p < 0.05$ for the secondary outcomes, however the trial was not powered to detect any treatment differences.

Post-hoc analysis

We undertook a post-hoc exploratory analysis to investigate the relationship between hepcidin and CRP concentrations at baseline (pre-randomisation), and Hb response at 28 days post-randomisation by study arm. We used similar methodology

to Steensma et al (27) and divided hepcidin and CRP values into tertiles which were compared with Hb responses at 28 days post-randomisation. We also compared the prevalence of different categories of anaemia at 28- and 90-days post randomisation.

Results

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 17Sep2019 to 20Dec2020 with final patient follow-up completed on 13Mar2020. A CONSORT flowchart summarising patient recruitment is shown in **Figure 1**. Reasons for ineligibility are detailed in **Supplementary Table 6**. Patient characteristics were similar at baseline (**Table 1**).

Primary outcomes

Feasibility outcomes are displayed in **Table 2**. A total of 606 patients were screened, and of the 290 (48%) that were eligible for recruitment, 98 (34%) were randomised over 15 months. Forty-seven out of 49 (96%) participants received the intervention and all HRQoL data were collected for 79/93 (85%) survivors at the 90 day follow-up visit. Overall, INTACT met the 'amend' criterion for recruitment and the 'go' criteria for protocol adherence and completion of HRQoL questionnaires (**Supplementary Table 4)**. Details on individual centre recruitment rates and reasons for missing outcome data are shown in **Supplementary Tables 7 and 8,** respectively. Ferric carboxymaltose was well tolerated and there were no serious adverse events.

Secondary outcomes

Clinical and HRQoL outcomes are summarised in **Table 3.** There were no statistically significant differences in in-hospital mortality and nosocomial infection rates between the study groups. The median (IQR) post-ICU hospital LOS (days) was shorter in the IV iron group, but this did not reach statistical significance (5.0 (3.0 to 13.0) vs. 9.0 (5.0 to 16.0), p = 0.15). Hospital readmissions in the first 90 days following ICU discharge were lower in the IV iron group (7/40 (17.5%) vs. 15/39 (38.5%) RR (95% CI): 0.46 (0.21, 0.99)) **(Table 3)**. There was no evidence of an effect on overall HRQoL scores by treatment assignment.

Mean (SD) Hb (g/L) concentrations were higher in the IV iron group at 28 days (119.8 (13.3) vs. 106.7 (14.9)) and 90 days (130.5 (15.1) vs. 122.7 (17.3), adjusted mean difference (95% CI) 11.0 (5.0 to 17.0) g/L, p <0.001) post-

randomisation. IV iron also resulted in higher ferritin, iron and Tsat concentrations up to 90 days when compared with usual care (**Figure 2 and Supplementary Table 9).** There was no evidence of a treatment difference in hepcidin concentrations at 28 days but median (IQR) hepcidin concentrations were lower in the usual care group at 90 days when compared with IV iron (13.9 (3.6-33.3) ng/mL vs. 35.0 (7.6-60.1) ng/mL, p=0.048) (**Supplementary Figure 1 and Supplementary Table 10**). EPO concentrations were lower in the IV iron group during the study follow up period but there was no evidence of an effect on serum phosphate, CRP and sTfR concentrations. Using previously accepted definitions of systemic inflammation [28], 12/38 (31.6%) participants in the usual care group and 8/31 (25.8%) in the IV group had a CRP concentration >10 mg/L at 90 days.

Post-hoc analyses

Numerically, more participants had Hb ≤100 g/L in the usual care group at 28 and 90 days post-randomisation (**Supplementary Table 11**). Participants with baseline serum hepcidin concentrations ≤ 20.2 ng/mL, and who received IV iron, experienced a greater median change in Hb when compared with usual care (45 vs 34 g/L) and had a higher median Hb at 28 days (127 vs 115 g/L) **(Supplementary Figure 3)**. The median Hb was lower in the usual care arm at 28 days in all hepcidin tertiles, with these effects more marked in participants with hepcidin concentrations >64.3 ng/mL (98 vs. 127 g/L). Similar effects were also observed for median Hb at 28 days when participants were stratified by baseline CRP levels (**Supplementary Figure 4**).

Discussion

Key findings

We confirm the feasibility of conducting a multicentre trial of IV iron in ICU survivors with moderate and severe anaemia. Protocol compliance was good, and HRQoL outcome data were available for over 80% of surviving participants at 90 days post-randomisation. IV iron was well tolerated without any signals of harm.

Meaning of the study

Our study cohort displayed the typical laboratory changes associated with AI. Persisting inflammation has been considered as a barrier to Hb recovery [5, 28] but our data suggest that this may be overcome with IV iron. IV iron resulted in a greater increase in Hb concentrations and iron stores which were maintained up to 90 days post-randomisation, even though approximately one-quarter of participants in this group still had evidence of ongoing inflammation at this time point.

Our exploratory analyses showed that participants with high hepcidin and CRP concentrations in the usual care arm at baseline demonstrated a blunted Hb recovery, which can be overcome with IV iron. These markers may help to identify a cohort who are likely to have persisting anaemia in the post-ICU period and may therefore benefit from more targeted management. The direction of effect pointed towards benefit for IV iron in reducing hospital LOS and hospital readmissions. ICU patients are at risk of developing secondary hospital-acquired infections with estimates ranging from 14 – 30% [29, 30]. IV iron increases the levels of circulating free iron which may be detrimental to the host by promoting pathogen growth but we observed no evidence of an effect of IV iron on infection.

Relationship to other studies

IV iron has been shown to result in improvements in Hb, functional performance and quality of life in other patients with AI such as chronic kidney disease (CKD) [31], heart failure [32] and inflammatory bowel disease [33], but there are no comparable published data in ICU survivors.

Recent observational studies have shown that higher discharge Hb is associated with reduced post-discharge mortality and improved exercise capacity in ICU survivors [3, 34]. Data from the perioperative literature suggests that untreated anaemia may impair physical recovery and increase hospital LOS and rates of hospital readmission [35-37]. Treating anaemia with IV iron may reduce LOS and hospital readmissions in patients undergoing major abdominal surgery [38, 39].

Strengths and limitations

Strengths of our multicentre trial include a published study protocol (20), predefined trial progression criteria, central randomisation, and high protocol adherence and follow-up completion rates. We utilised a multimodal approach to minimise missing data and selection bias from loss to follow-up. We obtained outcome data for a minimum of 70 participants in order to provide a reasonable estimate of the standard deviations for the sample size estimation of a definitive trial [40].

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 [41]. However, we observed no differences in HRQoL scores or completion rates between groups. Although the

participants enrolled into our study were broadly representative of the UK national cohort, they were also a heterogenous group and this may have diluted any potential benefits of IV iron. Our exploratory outcome results should be considered hypothesis-generating.

Implications for a future trial

We have identified a range of issues for the design of a future trial. We included patients with an ICU discharge Hb ≤100 g/L based on previous research, in both ICU and non-ICU patients, which found associations between this threshold and persisting anaemia [1], high levels of fatigue [7] and poor mobility [42]. IV iron is also likely to be more efficacious when Hb is being corrected from lower concentrations [43]. We identified particular biological characteristics (e.g. hepcidin and CRP concentrations) that may be associated with differential responses to treatments. A future trial should consider stratifying for these characteristics at the point of randomisation and/or inform pre-planned sub-group analyses.

We used a pragmatic one-off dose of 1000mg ferric carboxymaltose. We did not evaluate erythropoietin (EPO) in our trial. EPO, in combination with iron therapy, has been advocated for the treatment of anaemia of inflammation (3) but there is uncertainty regarding its effects in ICU patients [44, 45]. The participants enrolled into our trial were representative of a cohort with significant fatigue, as evidenced by low mean FACIT-F scores at ICU discharge. Fatigue may therefore be a reasonable patient-centred primary outcome. If we assume that fatigue is linked to Hb, then the optimal timepoint to evaluate fatigue would be when Hb separation is maximal. In our trial, this occurred at 28 days post-randomisation. Data from our trials can be used to derive power calculations for a future clinical trial and minimally important differences of greater than 3 points have been defined previously [46]. Assuming the mean (SD) FACIT-F score of 28.2 (10.3) in the usual care arm at 28 days post-ICU discharge, to detect an improvement from IV iron to a mean FACIT-F score of 31.2 at 90% power, allowing a 15% loss to follow-up, the required sample size for a definitive trial is 632 patients (316 participants per group). IV iron may also have beneficial effects on cardiopulmonary function, exercise capacity and immunity [47-49], all of which require further investigation in ICU patients. Future studies should consider using standardised definitions of infection and powering the trial to exclude a clinically important difference.

Conclusion

In summary, a large clinical trial to investigate the effects of IV iron on patient-centred outcomes in ICU survivors appears feasible. Further research may help identify biological and clinical characteristics associated with different responses to IV iron.

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INTACT Investigators and participating sites: Oxford University Hospitals NHS Foundation Trust (Paula Hutton, Archana Bashyal, George Chapman, Killian Donovan, Christie James); Edinburgh Royal Infirmary NHS Lothian (Nicola Rea, Sarah Clark, Lucy Barclay, Kate Priestley, David Hope, Corrienne McCulloch); Royal Berkshire Hospital (Nicola Jacques; Shauna Bartley; Parminder Bhachu).

Trial Oversight Group: Quentin Hill; Andrew Walden, Toby Richards

OCTRU: Joanna Black, Emma Haines, Lucy Eldridge

This study has been conducted as part of the portfolio of trials in the registered UKCRC Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. It will follow/has followed their Standard Operating Procedures ensuring compliance with the principles of Good Clinical Practice and the Declaration of Helsinki and any applicable regulatory requirements.

We would like to thank all the patients and their families who participated in this trial.

Contributions:

Design of the study: AS, SJD, IM, VSB, SRM, DMG, TJ, HD, PAR, JDY, TSW, SJS

Statistical analysis plan: IM, SJD, MC-J, AS

Data acquisition: AS, JS, TJ, KW, MCF, INTACT Investigators

Data analysis: AS, MC-J, SJD, SJS

All authors were involved in the interpretation of the data and the drafting of the manuscript.

Ethics declarations

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Conflicts of interest:

Peter A Robbins reports grants from Vifor Pharma, outside of the submitted work.

Hal Drakesmith reports grants from Vifor outside of submitted work, funding from and consultancy with Pfizer outside of submitted work, and funding from La Jolla Pharmaceutical Company outside of submitted work

Consent to participate

The signed consent forms for all participants included consent to publication of aggregate data.

Code availability

Requests for code should be made to the corresponding author and will be considered on an individual basis by the study management committee.

Availability of data and material

Requests for data should be made to the corresponding author. Each request requires a research proposal including a clear research question and proposed analysis plan. Requests will be considered on an individual basis and are subject to review and approval by the INTACT trial management committee and relevant human research ethics committees.

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Table 1. Patient characteristics at baseline

	Usual care (n = 49)	IV iron (n = 49)
Age, years, mean (SD)	58.9 (17.7)	61.4 (17.9)
Sex, n (%)		
Male	30 (61%)	28 (57%)
Female	19 (39%)	21 (43%)
APACHE II Score, mean (SD)	17.4 (7.5)	17.3 (7.3)
Weight, kg, mean (SD)	76.7 (16.5)	79.8 (19.6)
No. of Charlson Comorbidity Index categories, n (%)		
0	9 (18%)	10 (20%)
1	14 (29%)	11 (22%)
2 or more	26 (53%)	28 (57%)
ICU admission type, n (%)		
Elective operation	16 (33%)	18 (37%)
Emergency operation	18 (37%)	18 (37%)
Medical	15 (31%)	13 (27%)
ICU organ support requirements, n (%)		
Advanced respiratory support	26 (53%)	19 (39%)
Advanced cardiovascular support	17 (35%)	17 (35%)
Advanced renal support	1 (2%)	4 (8%)
ICU red blood cell transfusion requirements		
No. of patients transfused, n (%)	15 (31%)	21 (43%)
No. of RBC units per patient, mean (SD)	2.89 (2.7)	2.52 (1.5)
ICU length of stay at randomisation*, days		
< 7 days	37 (76%)	36 (73%)
≥7 days	12 (24%)	13 (27%)
Mean (SD)	5.1 (4.8)	5.6 (4.7)
Median (IQR)	3 (3 to 6)	4 (2 to 7)
History of anaemia prior to ICU admission, n (%)	2 (4%)	8 (16%)
Anaemia severity at randomisation*		
<80 g/l	11 (22%)	11 (22%)
80-100 g/l	38 (78%)	38 (78%)
Laboratory parameters Ɨ		
Haemoglobin*, g/L	85.8 (9.8)	86.4 (7.7)
Serum ferritin, µg/L, median (IQR)	358.1 (246.0 to 640.0)	370.6 (197.2 to 548.8)
Transferrin saturation, %, median (IQR)	12.0 (9.0 to 16.0)	11.0 (8.0 to 15.0)
Serum iron, µm/L, median (IQR)	4.3 (3.1 to 6.1)	4.0 (3.0 to 6.0)
CRP, mg/L	153.4 (103.0)	140.1 (85.7)
Erythropoietin, Miu/mL	55.9 (70.9)	67.1 (61.8)
Serum hepcidin[ǂ], ng/mL, median (IQR)	36.8 (18.2 to >81)	39.7 (17.4 to 72.8)
Soluble transferrin receptor, nmol/L	28.6 (15.0)	29.2 (14.0)
Serum creatinine, mmol/L, median (IQR)	65.0 (56.0 to 89.0)	65.0 (47.0 to 82.0)
Serum albumin, g/L	21.9 (4.4)	22.6 (4.8)
Phosphate, mmol/L	0.98 (0.30)	0.97 (0.2)

* Minimisation factors for the randomisation were anaemia severity and participant ICU length of stay

Ɨ Mean (SD) unless otherwise indicated

ǂ The hepcidin assay was unable to record measurements higher than 81, all participants with >81 were given a value of 85 and the median, IQR calculated these are included as >81 for the IQR if relevant

APACHE Acute Physiology and Chronic Health Evaluation; *ICU* Intensive Care Unit; *IQR* interquartile range; *IV* intravenous, *RBC* Red blood cell, *SD* standard deviation

Table 2. Primary Feasibility outcomes

Feasibility outcome	Eligible	Randomised	Rate (95% Confidence Interval)
Recruitment	290	98*	34% (28%, 40%)
	Expected	Completed	
Protocol adherence (intervention arm)			
Intervention arm	49	47†	96% (86%, 100%)
Usual care arm	49	49	100% (93%, 100%)
Completion of 90-day HRQoL questionnaires			
EuroQol-5D-5L (EQ-5D-5L)	93‡	81	87% (79%, 93%)
Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)	93	81	87% (79%, 93%)
Multidimensional Fatigue Inverntory-20 (MFI-20)	93	79	85% (76%, 92%)

*On average, 6.5 participants were recruitment per month over three centres

†49 participants were randomised to the intervention arm, one participant died and one withdrew before receiving the intervention

‡ Five participants had died (four whilst in-hospital and one in the community) before their 90-day timepoint

Table 3. Secondary clinical and health-related quality of life outcomes

Outcome	Usual care (n = 49)	IV iron (n = 49)	Effect estimate (95% CI) ǂ	*P* value
Clinical outcomes				
In-hospital mortality, n (%)	1 (2%)	3 (6%)	3.00 (0.32 to 27.9)	0.62[1]
Nosocomial infection, n (%)	13 (27%)	13 (27%)	1.00 (0.52 to 1.93)	1.00[2]
Infection site[*]*, n*				
Lung	5	7		
Gastrointestinal tract	4	4		
Skin	1	1		
Invasive device	0	0		
Bone/joint	0	0		
Other, unspecified	3	2		
Post-ICU LOS, days Ɨ				
Mean (SD)	12.94 (12.63)	11.86 (19.24)		
Median (IQR)	9.0 (5.0, 16.0)	5.0 (3.0, 13.0)		0.15[3]
Hospital readmission post-randomisation				
28 days§	6/36 (16.6%)	5/38 (13.1%)	0.79 (0.26 to 2.36)	0.67[2]
90 days§	15/39 (38.5%)	7/40 (17.5%)	0.46 (0.21 to 0.99)	0.037[2]

* Participants could report more than one infection site therefore absolute values are given

Ɨ Post-ICU hospital length stay calculated as the time from randomisation until hospital discharge

ǂ Unadjusted risk ratio and 95% Confidence interval

1 Fisher's Exact 2 Chi-squared 3 Mann-Whitney

§ At 28-days, 36 participants on usual care arm and 38 participants on intravenous iron arm provided hospital readmission data. At 90 days, 39 participants on usual care arm and 40 participants on intravenous iron arm provided hospital readmission data

ICU Intensive care unit, *IV* intravenous, *LOS* Length of stay, *SD* Standard deviation, *IQR* interquartile range

Health-related quality of life outcomes							
	N[*]	Mean (SD)	N[*]	Mean (SD)	Mean difference (95% CI)ǂ	Adjusted mean difference (95% CI)§	
EuroQol-5D-5L Utilities							
Baseline	49	0.174 (0.367)	48	0.215 (0.378)			
28 Days	37	0.529 (0.308)	42	0.528 (0.333)			
90 Days	41	0.589 (0.287)	45	0.562 (0.365)	0.000070 (-0.101, 0.101)	-0.00149 (-0.119, 0.116)	0.98
EuroQol-5D-5L Visual Analogue Scale (VAS)							
Baseline	49	41.78 (23.08)	49	44.14 (24.31)			
28 Days	36	62.22 (16.81)	39	60.08 (21.25)			

90 Days	40	64.43 (18.32)	41	70.00 (18.84)	-2.02 (-4.44, 0.40)	-2.31 (-5.55, 0.93)	0.16
Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)							
Baseline	49	16.86 (12.54)	49	16.69 (12.73)			
28 Days	36	28.22 (10.28)	39	28.18 (11.19)			
90 Days	40	30.90 (13.16)	41	34.37 (12.26)	-0.16 (-4.80, 4.49)	-0.18 (-4.89, 4.53)	0.94
Multidimensional Fatigue Inventory-20 (MFI-20)							
MFI-20 Physical							
Baseline	49	13.49 (2.96)	49	13.29 (3.08)			
28 Days	36	14.06 (2.03)	38	13.71 (2.35)			
90 Days	39	13.54 (1.88)	40	13.33 (2.44)	-0.30 (-2.83, 2.22)	-0.26 (-2.56, 2.04)	0.82
MFI-20 Mental							
Baseline	49	11.78 (3.89)	49	12.10 (2.93)			
28 Days	36	11.31 (2.86)	38	11.16 (2.09)			
90 Days	39	11.54 (2.51)	40	11.13 (2.29)	-0.13 (-1.09, 0.83)	-0.10 (-1.10, 0.90)	0.85
MFI-20 Reduced Activity							
Baseline	49	13.76 (3.00)	49	13.33 (3.11)			
28 Days	36	13.75 (2.02)	38	13.39 (2.25)			
90 Days	39	12.87 (1.89)	40	12.75 (2.62)	-0.28 (-1.70, 1.13)	-0.27 (-1.64, 1.11)	0.70
MFI-20 General							
Baseline	49	12.02 (3.38)	49	12.24 (3.21)			
28 Days	36	11.14 (2.51)	38	10.95 (2.14)			
90 Days	39	10.87 (2.14)	40	11.20 (2.00)	-0.25 (-0.76, 0.26)	-0.25 (-0.77, 0.26)	0.34
MFI-20 Reduced motivation							
Baseline	49	12.47 (3.67)	49	12.43 (3.30)			
28 Days	36	12.28 (2.94)	38	12.37 (2.73)			
90 Days	39	12.69 (2.57)	40	12.40 (2.75)	0.15 (-0.14, 0.44)	0.18 (-0.15, 0.51)	0.28

* Number of participants with available data

ǂ Mixed effect model with time treatment interaction and time as a categorical variable, adjusted for baseline values with cluster robust standard errors for centres

§ Mixed effect model with time treatment interaction and time as a categorical variable , adjusted for baseline values, minimisation factors(haemoglobin and length of stay in ICU at randomisation as continuous) with cluster robust standard errors for centres

IQR interquartile range, *SD* Standard deviation,

Higher scores indicate better quality of life for MFI and EQ-5D (Utilities and VAS), higher scores represent better function or less fatigue for FACIT-F

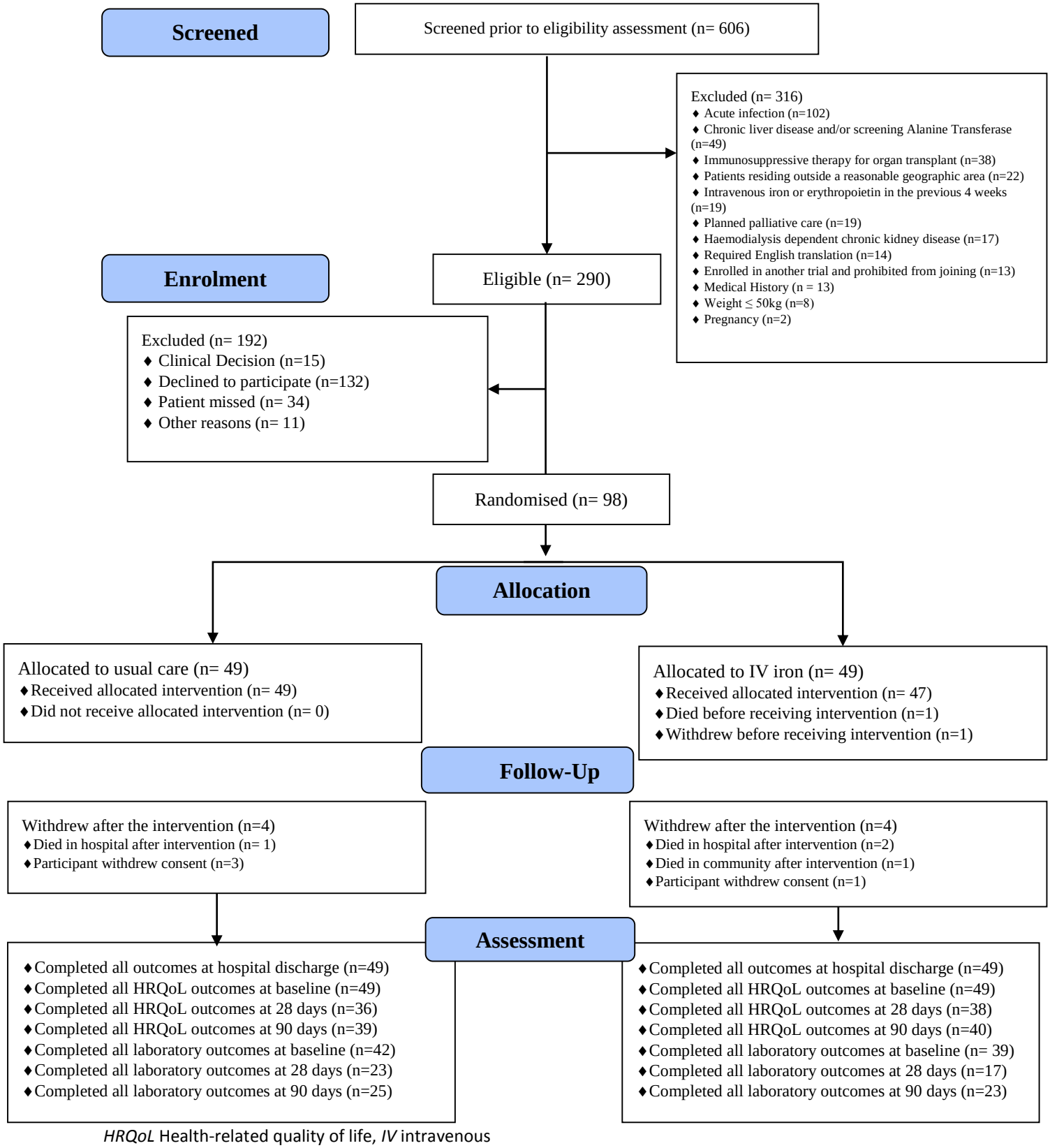
Figure legends

Figure 1. CONSORT Flow Diagram of participants throughout the trial.

Figure 2. Mean and 95% confidence interval at baseline, 28 days and 90 days post-randomisation in (A) haemoglobin, (B) ferritin, (C) transferrin saturation and (D) serum iron concentrations. Mean (SD) Hb (g/L) concentrations were higher in the IV iron group at 28 days (119.8 (13.3) vs. 106.7 (14.9)) and 90 days (130.5 (15.1) vs. 122.7 (17.3), adjusted mean difference (95% CI) 11.0 (5.0 to 17.0) g/L, $p < 0.001$) post-randomisation. IV iron also resulted in higher ferritin, iron and Tsat concentrations up to 90 days when compared with usual care.

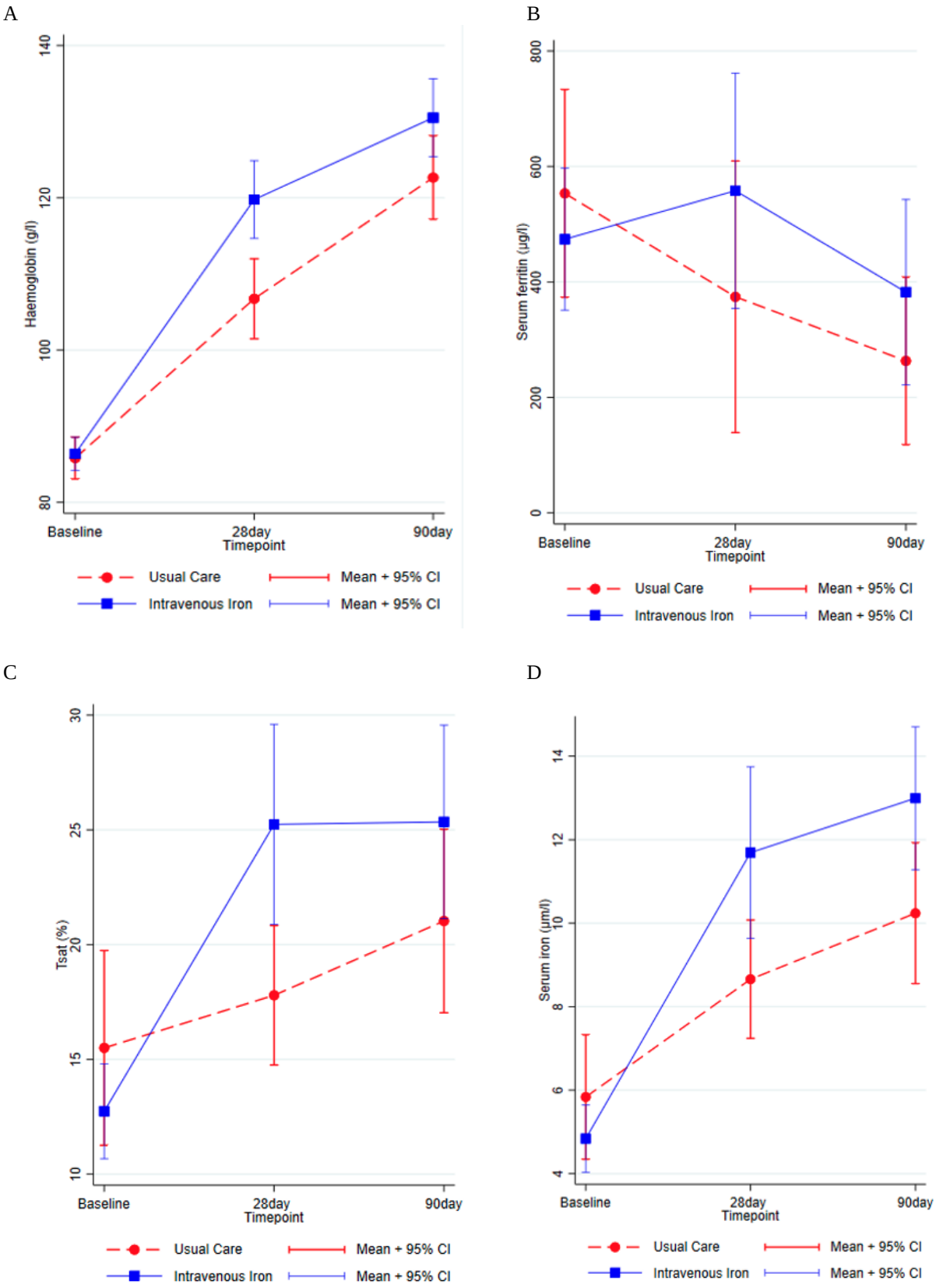
Figures

Figure 1. CONSORT Flow Diagram of participants throughout the trial.



HRQoL Health-related quality of life, *IV* intravenous

Figure 2. Mean and 95% confidence interval at baseline, 28 days and 90 days post-randomisation in (A) haemoglobin, (B) ferritin, (C) transferrin saturation and (D) serum iron concentrations



Cover Letter

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AUTHORSHIP AND CONFLICT OF INTEREST STATEMENT

The undersigned authors declare that the **authorship roles** and **conflict of interest** statements reported in the manuscript are correct and true.

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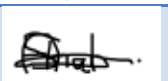
1	Akshay	Shah	Akshay.shah@linacre.ox.ac.uk	
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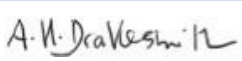
4	Hal	Drakesmith	Alexander.drakesmith@ndm.ox.ac.uk	
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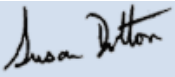
7	Susan	Dutton	Susan.dutton@csm.ox.ac.uk	
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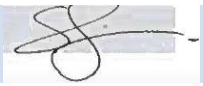
9	Jo	Singleton	Jo.singleton@nhslothian.scot.nhs.uk	
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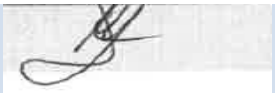
15	Tim	James	Tim.james@ouh.nhs.uk	
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