Professor Iain Moppett,

Anaesthesia and Critical Care Section,

Division of Clinical Neuroscience,

University of Nottingham (Queen's Medical Centre Campus),

Nottingham University Hospitals NHS Trust,

Derby Road, Nottingham, NG7 2UH.

The effect of intravenous iron on erythropoiesis in older people with hip fracture

I.K. Moppett [1], M. Rowlands[2], A. M. Mannings[3], T. C. Marufu[4], O. Sahota [5] and J. Yeung [6]

1 Professor and Honorary Consultant Anaesthetist, Anaesthesia and Critical Care Research Group, Division of Clinical Neuroscience, Queen's Medical Centre, University of Nottingham, UK. Iain.moppett@nottingham.ac.uk @IainMoppett

2 Consultant Anaesthetist, Department of Anaesthesia, Sheffield Teaching Hospitals NHS Foundation Trust martin.rowlands@sth.nhs.uk

3Consultant Anaesthetist, Department of Anaesthesia, Sheffield Teaching Hospitals NHS Foundation Trust alexa.mannings@sth.nhs.uk

4 Clinical Nurse Educator, Department of Healthcare of Older Life, Nottingham University Hospitals NHS Trust takawira.marufu@nuh.nhs.uk

5 Consultant and Honorary Professor of Ortho-Geriatric Medicine, Nottingham University Hospitals NHS Trust opinder.sahota@nuh.nhs.uk

6 Associate Professor and Honorary Consultant in Anaesthesia and Intensive Care, Warwick Medical School, University of Warwick, UK. J.yeung.4@warwick.ac.uk @yeung_joyce

Corresponding author: Professor I. K. Moppett

Email: iain.moppett@nottingham.ac.uk

Key words:

Erythropoiesis

Iron

Anaemia

Blood Transfusion

Hip Fractures

Key points:

Intravenous iron administered following hip fracture has a modest effect on erythropoiesis.

The effect of intravenous iron on haemoglobin is too delayed to affect hospital-based outcomes such as transfusion rates and return to home.

It is unlikely that intravenous iron will have a clinically significant benefit on longer-term outcomes.

Summary

Background: Anaemia following hip fracture is common and associated with worse outcomes. Intravenous iron is a potential non-transfusion treatment for this anaemia and has been found to reduce transfusion rates in previous observational studies. There is good evidence for its use in elective surgical populations.

Objective: to examine the impact of intravenous iron on erythropoiesis following hip fracture.

Design: two-centre, assessor-blinded, randomised, controlled trial of patients with primary hip fracture and no contra-indications to intravenous iron.

Method: The intervention group received three doses of 200mg iron sucrose over 30 minutes (Venofer, Vifor Pharma, Bagshot Park, UK) on three separate days. Primary outcome was reticulocyte count at day 7 after randomisation. Secondary outcomes included haemoglobin concentration, complications and discharge destination. Eighty participants were randomised.

Results: There was a statistically significantly greater absolute final reticulocyte count in the iron group (89.4 (78.9 - 101.3) x 10^9 cells.l^{-1} (n = 39) vs the control (72.2 (63.9 – 86.4)) x 10^9 cells.l^{-1} (n = 41); p = 0.019; (mean (95% confidence intervals) of log transformed data). There were no differences in final haemoglobin concentration (99.9 (95.7 – 104.2) vs 102.0 (98.7 - 105.3) p = 0.454) or transfusion requirements in the first week (11 (28%) vs 12 (29%); p = 0.899). Functional and safety outcomes were not different between the groups.

Conclusions: Although intravenous iron does stimulate erythropoiesis following hip fracture in older people, the effect is too small and too late to affect transfusion rates.

Trial Registry Numbers

ISRCTN:76424792; EuDRACT: 2011-003233-34

Optimal blood management for people admitted with hip fracture remains unclear. Around 30% of people are mildly anaemic on admission and 10% moderately anaemic (haemoglobin concentration < 100 $g.l^{-1}$) [1]. Given the potential harms associated with blood transfusion, lack of convincing benefit [2], and significant cost, alternative approaches to mitigate the deleterious effects of anaemia are needed [3].

Oral iron is known to be ineffective [4]. Observational studies have suggested that intravenous iron may be beneficial in elective orthopaedic surgery and in people with hip fracture [5-10].

A single randomised-controlled trial of intravenous iron in hip fracture was inconclusive [11]. Before embarking on a larger trial, we therefore wished to answer the question: does early intravenous iron improve markers of erythropoiesis in a contemporary hip fracture population?

Methods

We conducted a prospective parallel group, randomised, controlled, assessor-blinded study across two English National Health Service (NHS) Hospitals. Details of regulatory approvals are given in Appendix 1 in the supplementary data on the journal website (www.academic.oup.com/ageing).

Full details of the protocol have been published previously [12]. The only change of significance was the addition of a second site to enhance recruitment in 2015.

Inclusion criteria were: ≥ 70 years old; emergency admission with primary fracture of the hip within previous 24 hours and able to gain written informed consent from the participant. Exclusions included severe infection on admission, liver disease, known sensitivity to intravenous iron, concomitant oral iron therapy, and taking clopidogrel. All participants gave written consent following receipt of written and verbal information.

Standard care

Standard care was the same for all participants, aiming to meet national standards (see Appendix 2).

Transfusion triggers

Intra- and immediate postoperative transfusion was at the discretion of the anaesthetist. Postoperative transfusion guidance was, in order of clinical priority:

- Ongoing blood loss with hypovolaemia;
- Symptomatic anaemia: anaemia with haemoglobin concentration < 100 $g.l^{-1}$ associated with persistent hypotension, angina, heart failure or cerebral dysfunction;
- Asymptomatic anaemia with haemoglobin concentration < 80 $g.l^{-1}$;
- Relative anaemia (haemoglobin concentration significantly less than normal for the patient) and poor functional recovery following surgery (in the view of the attending clinician) (This criterion was never used within the study).

Study intervention

Participants randomised to the intervention group received three doses of 200mg iron sucrose over 30 minutes (Venofer, Vifor Pharma, Bagshot Park, UK) on three separate occasions:

Day 1 (within 24 hours of admission);

Day 1 postoperative; or second morning following admission if not yet gone to theatre

Day 2 postoperative; or third morning following admission if not yet gone to theatre

Data collected

Basic participant characteristics on admission included: age, sex, admission source, admission and day one haemoglobin concentration, type of fracture, operation performed,

time from admission to surgery, reticulocyte index (proportion (%) of red blood cells that are reticulocytes). Full blood count and reticulocyte counts were taken on days 1 to 7 post-randomisation. Serum transferrin receptor concentrations were taken on days 1 and 7 post-randomisation. The Cumulated Ambulation Score [13, 14] was recorded on the first three post-operative days. Infective and cardiovascular complications were reported using the Post-operative Morbidity Survey criteria [15].

Randomisation, blinding and statistical analysis are described in Appendix 3. The primary outcome was absolute reticulocyte count on day 7. Secondary outcomes are detailed in appendix 4.

Funding and sources of support

This work was supported by a grant from the Association of Anaesthetists. There was no funding, support or involvement in any aspect of the study from the manufacturers of intravenous iron.

Results

Eighty patients were randomised, and primary outcome data were available for 73 participants (CONSORT summary in Appendix 5 figure 1).

All participants randomised to intravenous iron received at least one dose. Seven participants did not receive all three doses (3 only received one dose, 4 received two doses). The reasons for non-administration and incomplete primary data are detailed in Appendix 6.

Participant characteristics are shown in table 1 and in Appendix 7 supplementary tables 1B-F.

Table 1 Characteristics of patients included in the study.

There was a statistically significantly greater absolute final reticulocyte count in the iron group (89.4 (78.9 - 101.3) x 10^9 cells.l^{-1} (n = 35) vs the control (72.2 (63.9 – 86.4)) x 10^9 cells.l^{-1} (n = 37); p = 0.019; (mean (95% confidence intervals).

There were no statistically significant differences in final or maximum haemoglobin concentrations, nor in any measures of transfusion requirement. (Table 2 and Appendix 7, supplementary tables 2B-F). The changes in haematological indices over the first seven days are shown in Appendix 5 supplementary figures 2A-F.

Table 2 Haematological outcome measures.

There were no statistically significant differences between the groups in any other outcome measures. (Appendix 7, supplementary table 3).

Adverse events are detailed in Appendix 8.

Discussion

Intravenous iron stimulated erythropoiesis in patients in the first week following hip fracture. This was not translated into differences in haemoglobin concentration nor a

reduction in transfusion requirements. Functional outcomes were unchanged and there was no evidence of increased risk of infection or cardiovascular complications.

The participants were similar to previous studies of patients with hip fracture. The clinically relevant difference compared with the overall hip fracture population is that all participants had mental capacity, a lower risk group compared with those with dementia. The relatively low recruitment proportion might impact on the generalisability of the findings; regulatory approvals did not permit this drug study in people without capacity.

The groups were well matched and time to theatre was consistent with contemporary practice in the UK. Of note, this study again demonstrates the large decrease (approximately 27 $g.l^{-1}$) in haemoglobin seen following hip fracture, with extracapsular fractures having the greatest decrease (see appendices 5 & 7).

In contrast to previous observational studies, the increased reticulocyte production did not translate into greater haemoglobin concentrations nor reduced transfusion requirements.

The early post-operative transfusion rate was around 27%, lower than in previous studies. Seven days may be too early to see an effect on haemoglobin concentration. However, late transfusion (between day 7 and discharge) was uncommon – 2 out of 80 participants. If the effect on haemoglobin concentration is delayed, and late transfusion is relatively uncommon then there is little scope for intravenous iron to reduce transfusion requirements. The interval between admission and surgery was short. The opportunity for the erythropoietic effect of iron to influence transfusion in the perioperative and early postoperative phase is therefore limited.

At the trial development stage, iron sucrose, given as three divided doses, was chosen as the iron formulation. Five percent of participants declined to complete the three-day course of intravenous iron. Single dose formulations of ferric carboxymaltose are now available and

widely used. These might improve real-world effectiveness, requiring one administration, thereby ensuring a treatment dose is guaranteed. There are some data from long-term use with chronic kidney suggesting that greater erythropoietic efficacy is achieved with ferric carboxymaltose than with iron sucrose [16]. However, it is not clear whether this would translate into improved efficacy in the short-term context of post-hip fracture recovery. Although the role of tranexamic acid in hip fracture is still unresolved [17], it is an effective drug to reduce the need for early transfusion. There is an ongoing trial investigating the effect on transfusion rates of intravenous iron and / or tranexamic acid in hip fracture [18] but recruitment is not anticipated to finish until 2022.

Study recruitment took much longer than anticipated for a variety of reasons including change in study personnel. The finding that almost 30% of potential participants lacked sufficient capacity for a drug trial is not particularly surprising. However, the high refusal rate of eligible participants severely hampered recruitment, a factor that is known to impact on clinical studies of older people [19].

Our findings may have impact beyond the hip fracture population. First, we have demonstrated an erythropoietic effect of intravenous iron in older people following acute blood loss. This may have relevance to both in- and outpatient management of older people with blood loss not necessitating transfusion or resuscitation. Second, despite the admission low – normal haemoglobin, older people do demonstrate a reticulocyte response. With the caveat that this trial did not study the frailest of patients with hip fracture, older people can respond to acute production requirements, even in the presence of the suppressant effect of inflammation following injury and surgery.

In conclusion, intravenous iron is an effective drug for stimulating erythropoiesis in older people following hip fracture. With changes in hip fracture management, particularly earlier

surgery and lower transfusion thresholds, it is unlikely to be an effective approach to reducing transfusion requirements.

Acknowledgements are detailed in Appendix 6

References

1. Potter LJ, Doleman B, Moppett IK. A systematic review of pre-operative anaemia and blood transfusion in patients with fractured hips. *Anaesthesia* 2015; **70**: 483-500.
2. Carson JL, Terrin ML, Noveck H et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *New England Journal of Medicine* 2011; **365**: 2453-62.
3. Muñoz M, Acheson AG, Bisbe E et al. An international consensus statement on the management of postoperative anaemia after major surgical procedures. *Anaesthesia* 2018; **73**: 1418-31.
4. Parker MJ. Iron supplementation for anemia after hip fracture surgery: a randomized trial of 300 patients. Journal of Bone and Joint Surgery (American Edition) 2010; **92**: 265-269.
5. Muñoz M, Gómez-Ramírez S, Cuenca J et al. Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: a pooled analysis of observational data from 2547 patients. *Transfusion* 2014; **54**: 289-99.
6. Blanco Rubio N, Llorens Eizaguerri M, Seral García B, Burillo Fuertes P, Ranera García M, Albareda Albareda J. [Preoperative intravenous iron as a strategy for blood saving in surgery for hip fracture]. *Medicina Clínica* 2013; **141**: 371-375.
7. Garcia-Erce JA, Cuenca J, Munoz M et al. Perioperative stimulation of erythropoiesis with intravenous iron and erythropoietin reduces transfusion requirements in patients with hip fracture. A prospective observational study. *Vox Sanguinis* 2005; **88**: 235-243.

8. Cuenca J, García-Erce JA, Muñoz M, Izuel M, Martínez AA, Herrera A. Patients with pertrochanteric hip fracture may benefit from preoperative intravenous iron therapy: a pilot study. *Transfusion* 2004; **44**: 1447-52.
9. Cuenca JE, García-Erce JA, Martínez AAM, Solano VM, Modrego FJA. Safety and usefulness of parenteral iron in the management of anemia due to hip fracture in the elderly. *Medicina Clínica* 2004; **123**: 281-5.
10. Cuenca J, García-Erce JA, Martínez AA, Solano VM, Molina J, Munoz M. Role of parenteral iron in the management of anaemia in the elderly patient undergoing displaced subcapital hip fracture repair: preliminary data. *Archives of Orthopaedic and Trauma Surgery* 2005; **125**: 342-7.
11. Serrano-Trenas JA, Ugalde PF, Cabello LM, Chofles LC, Lázaro PS, Benítez PC. Role of perioperative intravenous iron therapy in elderly hip fracture patients: a single-center randomized controlled trial. *Transfusion* 2011; **51**: 97-104.
12. Rowlands M, Forward DP, Sahota O, Moppett IK. The effect of intravenous iron on postoperative transfusion requirements in hip fracture patients: study protocol for a randomized controlled trial. *Trials* 2013; **14**: 288.
13. Kristensen MT, Jakobsen TL, Nielsen JW, Jørgensen LM, Nienhuis R-J, Jønsson LR. Cumulated Ambulation Score to evaluate mobility is feasible in geriatric patients and in patients with hip fracture. *Danish Medical Journal* 2012; **59**: A4464.
14. Foss NB, Kristensen MT, Kehlet H. Prediction of postoperative morbidity, mortality and rehabilitation in hip fracture patients: the cumulated ambulation score. *Clinical Rehabilitation* 2006; **20**: 701-8.

15. Grocott MP, Browne JP, Van der Meulen J et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *Journal of Clinical Epidemiology* 2007; **60**: 919-28.

16. Hofman JMG, Eisenaga MF, Diepenbroek A et al. Switching iron sucrose to ferric carboxymaltose associates to better control of iron status in hemodialysis patients. *BMC Nephrology* 2018; **19**:242

17. Farrow LS, Smith TO, Ashcroft GP, Myint PK. A systematic review of tranexamic acid in hip fracture surgery. *British Journal of Clinical Pharmacology* 2016; **82**: 1458-70.

18. HiFIT Study : Hip Fracture: Iron and Tranexamic Acid (HiFIT) https://clinicaltrials.gov/ct2/show/NCT02972294 (accessed 26/02/2018).

19. Clegg A, Relton C, Young J, Witham M. Improving recruitment of older people to clinical trials: use of the cohort multiple randomised controlled trial design. *Age and Ageing* 2015; **44**: 547-50.

Tables

Table 1: Baseline characteristics of patients included in the study

	Control (n = 41)	**Iron (n = 39)**
Age (years)	82.5 (5.8)	81.2 (7.0)
Sex (male)	12 (29)	15 (39)
Admission source		
Home – Independent	36 (89)	36 (92)
Nursing care	0	1 (3)
Residential care	1 (2)	0
Warden controlled	4 (10)	2 (5)
Operation		
AO Screws	2 (5)	1 (3)
DHS	14 (34)	9 (23)
Hemiarthroplasty	18 (45)	22 (56)
Nail	2 (5)	4 (10)
Total Hip Arthroplasty	5 (12)	3 (8)
Fracture type (%)		
Extracapsular	17 (41)	13 (33)
Intracapsular	24 (59)	26 (67)
Time to theatre (hours)	29.8 (20)	29.7 (17)
Haemoglobin on admission		
log	4.83 (0.11)	4.81 (0.16)
$g.l^{-1}$	125.4 (121.4 - 129.6)	122.4 (116.5 - 128.6)
Haemoglobin on admission < 120 $g.l^{-1}$	15 (36.6)	16 (42.1)
Reticulocyte count day 1		
log	3.70 (0.28)	3.74 (0.30)
10^9 cell L^{-1}	40.4 (36.9 - 44.2)	42.2 (38.3 - 46.6)
Reticulocyte index day 1		
log	0.10 (0.32)	0.15 (0.36)
%	1.11 (1.00 - 1.23)	1.16 (1.03 - 1.3)
Haemoglobin day 1		
log	4.72 (0.18)	4.71 (0.20)
$g.l^{-1}$	112.7 (106.4 - 119.3)	111.1 (104.1 - 118.6)

Data are reported as mean (sd) or number (proportion). The mean (sd) for log transformed data are supplemented by the back-transformed mean (95% confidence interval). Day 1 is the day of consent and randomization, so haematological data are all before administration of iron.
AO screws – parallel screw fixation; DHS – dynamic hip screw.

Table 2: Haematological outcomes

Outcome	**Control (n = 41)**	**Iron (n = 39)**	**p**
Reticulocytes final day	(n = 37)	(n = 35)	
log	4.28 (0.38)	4.49 (0.38)	0.019
10^9 cells.l^{-1}	72.2 (63.9 - 86.4)	89.4 (78.9 - 101.3)	
Reticulocytes day 7	(n = 30)	(n = 29)	
log	4.33 (0.36)	4.51 (0.37)	0.056
10^9 cells.l^{-1}	75.8 (66.5 - 86.4)	91.2 (79.8 - 104.2)	
Reticulocyte index final day	(n = 37)	(n = 35)	
log	0.77 (0.42)	0.99 (0.35)	0.022
%	2.19 (1.91 - 2.51)	2.69 (2.39 - 3.03)	
Reticulocyte index day 7	(n = 30)	(n = 29)	
log	0.82 (0.42)	1.00 (0.33)	0.069
%	2.28 (1.97 - 2.64)	2.73 (2.42 - 3.08)	
Haemoglobin final day	(n = 38)	(n = 36)	
log	4.60 (0.14)	4.62 (0.10)	0.454
g.l^{-1}	99.9 (95.7 – 104.2)	102.0 (98.7 - 105.3)	
Haemoglobin day 7	(n = 33)	(n = 29)	
log	4.61 (0.14)	4.64 (0.09)	0.466
g.l^{-1}	100.9 (96.4 - 105.6)	103.2 (99.7 - 106.8)	
Minimum haemoglobin first 7 days			
log	4.51 (0.16)	4.52 (0.14)	0.638
g.l^{-1}	90.6 (86.1 - 95.2)	92.1 (88.0 - 96.2)	
Maximum fall in haemoglobin first 7 days			
log	3.39 (0.69)	3.23 (0.74)	0.344
g.l^{-1}	29.5 (23.9 - 36.5)	25.3 (20.0 - 32.1)	
Maximum reticulocytes first 7 days			
log	4.29 (0.34)	4.49 (0.36)	0.022
10^9 cells.l^{-1}	72.7 (66.5 – 80.6)	88.8 (79.3 - 99.4)	
Maximum reticulocyte index first 7 days			
log	0.78 (0.40)	0.97 (0.36)	0.022
%	2.17 (1.92 - 2.46)	2.63 (2.35 - 2.94)	
Serum Transferrin Receptor Concentration final day (mg.l^{-1})	(n = 29) 17.4 (14.5 - 19) [10.1 - 24.8]	(n= 26) 16.1 (14.1 - 17.9) [9.3 - 24.8]	0.418
Total transfusions during admission	0 (0 - 1) [0 - 4]	0 (0 - 1) [0 - 4]	0.927
Participants transfused during admission	12 (29)	11 (28)	1.000
Total transfusions in first week	0 (0 - 1) [0 - 4]	0 (0 - 1) [0 - 4]	0.899
Participants transfused during first week	11 (27)	11 (28)	1.000

Data are reported as mean (sd), median (interquartile range) [range], or number (proportion). The mean (sd) for log transformed data are supplemented by the back-

transformed mean (95% confidence interval). P values are two-side tests on the log-transformed data, chi-squared tests on proportions and Mann-Whitney-U tests on non-parametric data as appropriate. In cases of missing outcome data, the group totals are shown; all other outcomes were for all participants.

Appendix 1

Regulatory information:

Study recruitment commenced in 18th July 2012 and ended on 22nd July 2017. Relevant approvals were obtained: Nottingham Research Ethics Committee on 23 November 2011 (reference number 11/EM/0310); the Nottingham University Hospitals Research and Development department on 2 August 2011 (reference number 68213), Birmingham Heartlands Research and Development department on 16 April 2014; and the UK Medicines and Healthcare products Regulatory Authority on 19 January 2012, (EuDRACT: 2011-003233-34). The study was also registered with the National Institute for Health Research Portfolio and ISRCTN:76424792 (10 September 2012). The study complied with Good Clinical Practice standards set forth in the Declaration of Helsinki of 1975.

Appendix 2

Standard care

Standard care was the same for all participants, aiming to meet national standards as set out by the National Institute of Clinical Excellence (CG124) [1]; Best Practice Tariff [2, 3], British Orthopaedic Society Standard for Trauma [4], and Association of Anaesthetists [5]. This included fast-track admission for most patients, an integrated hip fracture pathway, surgery within 36 hours on a dedicated orthopaedic trauma list with senior surgeons and anaesthetists, and shared care with consultant ortho-geriatricians. Surgical and anaesthetic treatment options were at the discretion of the surgeons and anaesthetists and were not affected by the study.

Tranexamic acid was not routinely used during the period of the study. Wound drains were not routinely used, nor were pressure dressings. Autologous transfusion was not used.

Appendix 3

Randomisation and blinding

Participants were randomised on a one-to-one basis to standard care or intravenous iron. Randomisation was performed using a password-controlled, web-based randomisation service (Nottingham Clinical Trials Unit) with random block sizes and the sequence was kept blinded until data-lock.

Participants were not blinded to allocation (intravenous iron is an unmistakeable bright orange). Blood tests were ordered, and results obtained, without any reference to group allocation. Mobility assessments and discharge arrangements were performed by physiotherapists and clinical staff uninvolved with the study.

Statistical approaches

All calculations were performed using R statistical package [6]. Descriptive statistics were used for demographic data.

Log transformation was used to enable parametric testing as appropriate; means and confidence intervals are back transformed to the natural units. In cases of missing haematological data at day 7, last value (day 6) was carried forward (referred to as 'final day'). Missing Cumulated Ambulation Scores were imputed as last value carried forward.

Power analysis was performed based on previous studies of intravenous iron in hip fracture. Garcia-Erce [7] demonstrated an absolute difference in reticulocyte index of 1.75% with standard deviation of 1.6%. A study of 70 participants would provide 80% power for detecting a difference of 1.0%. This equates to a relative difference in absolute reticulocyte count of 40 x 10^9 cell.l^{-1}. An extra 10 participants were planned to allow for drop-outs. The study was not powered for secondary outcomes.

Appendix 4

Secondary outcomes

Secondary haematological outcomes were:

Absolute reticulocyte count, reticulocyte index (proportion of red cells that are reticulocytes), and haemoglobin concentration daily in the first seven days after randomisation.

Serum transferrin receptor concentrations at day 7.

Transfusion requirements. Number of participants transfused, and units transfused per participants: during admission, in first seven days, in first 7 days excluding pre- and intra-operative transfusion.

Functional and safety outcomes included proportions of participants with infective and cardiovascular complications, length of hospital stay, and thirty-day mortality.

Appendix 5

Figures – see separate file

Appendix 6

Non-administration and incomplete data

The reasons for non-administration of intravenous iron doses were: patient refusal (itching, stinging at cannula site, blurred vision, no reason recorded); pyrexia > 38.5℃ (2 participants) and systemic illness.

Three participants were discharged before final reticulocyte counts were collected, two were not taken for unknown reasons, one patient's ward was closed to non-essential (research) staff and one participant declined to have blood samples taken but consented to follow-up and use of data.

Appendix 7

Tables – see separate file

Appendix 8

Adverse events

Ten serious adverse events were reported. Three deaths in the intravenous iron group were reviewed by an independent senior academic outside of the study team's department who felt none of the deaths were attributable to the study or directly related to intravenous iron. One episode of cardiac arrhythmia and two episodes of hospital acquired pneumonia were attributed as possibly related to intravenous iron; all three resolved.

Appendix 9

Acknowledgements

The authors thank the Department for Research and Education in Emergency and Acute Medicine and Major Trauma (**DREEAM**) at Nottingham University Hospitals, and Academic Department of Anaesthesia, Critical Care, Pain and Resuscitation team at Birmingham Heartlands Hospital for their support throughout the study.

The authors also thank Dr J P Moppett, Consultant Paediatric Haematologist for advice on longer-term haematological implications.

References for supplementary information

1. National Institute for Health and Care Excellence. Hip fracture: management. CG 124. 2017. Available from https://www.nice.org.uk/guidance/cg124 (accessed 10/12/2018).
2. Department of Health. *Payment by results guidance for 2010–11*. Leeds: Payment by Results team, Department of Health, 2010
3. Department of Health. *Payment by results guidance for 2013–14*. Leeds: Payment by Results Team, Department of Health, 2013
4. British Orthopaedic Association (BOA). The Care of Patients with Fragility Fracture, 2007. Available from https://www.bgs.org.uk/resources/care-of-patients-with-fragility-fracture-blue-book (accessed 10/12/2018).
5. White SM, Griffiths R, Holloway J, Shannon A. Anaesthesia for proximal femoral fracture in the UK: first report from the NHS Hip Fracture Anaesthesia Network. *Anaesthesia* 2010; **65**: 243-8.
6. The R Project for Statistical Computing 2016. Available from http://www.r-project.org/ (accessed 10/12/2018).
7. Garcia-Erce JA, Cuenca J, Munoz M et al. Perioperative stimulation of erythropoiesis with intravenous iron and erythropoietin reduces transfusion requirements in patients with hip fracture. A prospective observational study. *Vox Sanguinis* 2005; **88**: 235-243.

Appendix 7: Supplementary Tables
BASELINE CHARACTERISTICS

Table 1B
Characteristics of transfused participants

	Control (n = 11)	Iron (n = 11)
Age (years)	82.9 (4.66)	83.2 (8.22)
Sex (Male)	4 (36.4)	4 (36.4)
Admission source		
Home - Independent	10 (91)	9 (82)
Nursing care	0 (0.0)	1 (9)
Residential care	1 (9)	0 (0)
Warden controlled	0 (0)	1 (9)
Operation (%)		
AO Screws	0	0
DHS	7 (64)	2 (18)
Hemiarthroplasty	3 (27)	5 (46)
Nail	1 (9)	2 (18)
Total hip arthroplasty	0 (0)	2 (18)
Fracture type (%)		
Extracapsular	9 (82)	4 (36)
Intracapsular	2 (18)	7 (64)
Time to theatre (hours)	28.3 (17.2)	34.0 (24.2)
Haemoglobin on admission		
log	4.79 (0.16)	4.68 (0.14)
$g.l^{-1}$	120.4 (109.7 - 132.2)	108.3 (99.7 - 117.7)
Haemoglobin on admission < 120 $g.l^{-1}$	6 (54.5)	8 (72.7)
Reticulocyte count day 1		
log	3.70 (0.22)	3.68 (0.34)
10^9 $cell.l^{-1}$	40.4 (35.4 - 46.3)	39.7 (32.0 - 49.1)
Reticulocyte index day 1		
log	0.26 (0.35)	0.27 (0.44)
%	1.29 (1.03 - 1.62)	1.32 (1.00 - 1.73)
Haemoglobin day 1		
log	4.61 (0.21)	4.55 (0.23)
$g.l^{-1}$	100.5 (88.0 - 114.7)	94.3 (82.5 - 107.92)

Data are reported as mean (sd) or number (proportion). The mean (sd) for log transformed data are supplemented by the back-transformed mean (95% confidence interval). Day 1 is the day of consent and randomization, so haematological data are all before administration of iron.
AO screws – parallel screw fixation; DHS – dynamic hip screw.

Table 1C

Characteristics of non-transfused participants

	Control (n = 30)	Iron (n = 28)
Age (years)	82.4 (6.3)	80.4 (6.4)
Sex (Male)	8 (26.7)	11 (39.3)
Admission source		
Home - Independent	26 (87)	27 (96)
Nursing care	0	0
Residential care	0	0
Warden controlled	4 (13)	1 (4)
Operation (%)		
AO Screws	2 (7)	1 (4)
DHS	7 (23)	7 (25)
Hemiarthroplasty	15 (50)	17 (61)
Nail	1 (3)	2 (7)
THR	5 (17)	1 (4)
Fracture type (%)		
Extracapsular	8 (27)	2 (32)
Intracapsular	22 (73)	19 (68)
Time to theatre (hours)	30.4 (21.5)	28.1 (14)
Haemoglobin on admission		
log	4.85 (0.08)	4.86 (0.14)
$g.l^{-1}$	127.3 (123.7 - 131.0)	128.4 (122.1 - 135.1)
Haemoglobin on admission < 120 $g.l^{-1}$	9 (30)	8 (29)
Reticulocyte count day 1		
log	3.70 (0.31)	3.77 (0.29)
10^9 $cell.l^{-1}$	40.3 (36.0 - 45.2)	43.3 (38.7 - 48.3)
Reticulocyte index day 1		
log	0.05 (0.29)	0.09 (0.31)
%	1.05 (0.94 - 1.17)	1.1 (0.97 - 1.24)
Haemoglobin day 1		
log	4.77 (0.14)	4.78 (0.15)
$g.l^{-1}$	117.6 (111.4 - 124.1)	119.1 (112.6 – 126.0)

Table 1D

Characteristics of participants admitted with haemoglobin < 120 $g.l^{-1}$

	Control (n= 15)	Iron (n = 16)
Age (years)	83.9 (5.1)	80.9 (7.9)
Sex (Male)	3 (20)	4 (25)
Admission source		
Home - Independent	12 (80)	15 (94)
Nursing care	0	0
Residential care	1 (7)	0
Warden controlled	2 (13)	1 (6)
Operation (%)		
AO Screws	0	1 (6)
DHS	7 (47)	3 (19)
Hemiarthroplasty	5 (33)	8 (50)
Nail	1 (7)	3 (19)
THR	2 (13)	1 (6)
Fracture type (%)		
Extracapsular	8 (53)	6 (37)
Intracapsular	7 (47)	10 (63)
Time to theatre (hours)	32.2 (27)	24.7 (12
Haemoglobin on admission		
log	4.73 (0.07)	4.65 (0.09)
$g.l^{-1}$	113.7 (109.5 - 118.1)	104.4 (99.7 - 109.4)
Haemoglobin on admission < 120 $g.l^{-1}$	15 (100.0)	16 (100.0)
Reticulocyte count day 1		
log	3.65 (0.29)	3.60 (0.33)
10^9 $cell.l^{-1}$	38.3 (32.9 - 44.5)	36.7 (30.9 - 43.7)
Reticulocyte index day 1		
log	0.18 (0.36)	0.14 (0.44)
%	1.19 (0.98 - 1.45)	1.15 (0.92 - 1.45)
Haemoglobin day 1		
log	4.61 (0.19)	4.57 (0.18)
$g.l^{-1}$	100.3 (90.9 - 110.6)	96.1 (88.2 - 104.8)

Table 1E

Characteristics of participants with intracapsular fractures

	Control (n = 24)	Iron (n = 26)
Age (years)	82.0 (6.4)	80.4 (6.5)
Sex (Male)	6 (25)	11 (42)
Admission source		
Home - Independent	20 (83)	24 (92)
Nursing care	0	0
Residential care	0	0
Warden controlled	4 (17)	2 (8)
Operation (%)		
AO Screws	2 (8)	1 (4)
DHS	0	0
Hemiarthroplasty	17 (71)	22 (85)
Nail	0	0
Total hip arthroplasty	5 (21)	3 (12)
Time to theatre (hours)	30.0 (17)	31.9 (18.2)
Haemoglobin on admission		
log	4.85 (0.08)	4.82 (0.16)
$g.l^{-1}$	127.3 (123.2 - 131.5)	123.6 (116.3 - 131.4)
Haemoglobin on admission < 120 $g.l^{-1}$	7 (29)	10 (39)
Reticulocyte count day 1		
log	3.70 (0.30)	3.70 (0.29)
10^9 $cell.l^{-1}$	40.4 (35.5 - 45.9)	40.6 (36.1 - 45.6)
Reticulocyte index day 1		
log	0.02 (0.29)	0.08 (0.32)
%	1.02 (0.89 - 1.16)	1.08 (0.94 - 1.24)
Haemoglobin day 1		
log	4.78 (0.15)	4.75 (0.19)
$g.l^{-1}$	119.4 (112.0 - 127.2)	115.5 (107.2 - 124.4)

Table 1F

Characteristics of participants with extracapsular fractures

	Control (n = 17)	Iron (n = 13)
Age (years)	83.4 (5.1)	82.6 (7.9)
Sex (Male)	6 (35)	4 (31)
Admission source		
Home - Independent	16 (94)	12 (92)
Nursing care	0	1 (8)
Residential care	1 (6)	0
Warden controlled	0	0
Operation (%)		
AO Screws	0	0
DHS	14 (82)	6 (69)
Hemiarthroplasty	1 (6)	0
Nail	2 (12)	4 (31)
THR	0	0
Time to theatre (hours)	29.5 (24.4)	25.5 (15.0)
Haemoglobin on admission		
log	4.81 (0.14)	4.79 (0.16)
$g.l^{-1}$	122.9 (115.2 - 131.1)	120 (110.1 - 130.7)
Haemoglobin on admission < 120 $g.l^{-1}$	8 (47)	6 (46)
Reticulocyte count day 1		
log	3.70 (0.27)	3.82 (0.32)
10^9 $cell.l^{-1}$	40.4 (35.6 - 45.8)	45.7 (38.1 - 54.8)
Reticulocyte index day 1		
log	0.21 (0.32)	0.27 (0.40)
%	1.24 (1.05 – 1.46)	1.31 (1.04 – 1.64)
Haemoglobin day 1		
log	4.64 (0.18)	4.64 (0.22)
$g.l^{-1}$	103.5 (94.4 – 113.5)	103.5 (91.8 – 116.6)

OUTCOMES

Table 2B
Haematological outcomes for participants transfused in the first seven days

	Control (n = 11)	Iron (n = 11)	p
Reticulocytes final day			
log	4.39 (0.38)	4.35 (0.44)	0.852
10^9 cells.l^{-1}	80.4 (64.3 - 100.6)	77.8 (59.8 - 101.2)	
Reticulocytes day 7	(n = 8)	(n = 9)	
log	4.42 (0.42)	4.41 (0.44)	0.967
10^9 cells.l^{-1}	82.8 (61.7 – 111.1)	82.1 (61.7 - 109.1)	
Reticulocyte index final day			
log	0.95 (0.43)	0.86 (0.39)	0.614
%	2.58 (2.01 - 3.33)	2.36 (1.88 - 2.97)	
Reticulocyte index day 7			
log	1.01 (0.46)	0.93 (0.36)	0.677
%	2.76 (2.01 - 3.79)	2.54 (2.01 - 3.2)	
Haemoglobin final day			
log	4.55 (0.10)	4.62 (0.08)	0.097
$g.l^{-1}$	94.7 (89.4 - 100.3)	101.3 (96.4 - 106.5)	
Haemoglobin day 7	(n = 9)	(n = 9)	
log	4.53 (0.09)	4.62 (0.09)	0.061
$g.l^{-1}$	93.0 (87.9 - 98.4)	101.4 (95.3 - 107.8)	
Minimum haemoglobin first 7 days			
log	4.38 (0.20)	4.39 (0.12)	0.895
$g.l^{-1}$	79.9 (70.8 - 90.1)	80.6 (74.9 - 86.7)	
Maximum fall in haemoglobin first 7 days			
log	3.35 (1.20)	3.00 (1.04)	0.466
$g.l^{-1}$	28.5 (14.0 - 57.9)	20.0 (10.8 - 36.9)	
Maximum reticulocytes first 7 days			
log	4.40 (0.38)	4.43 (0.41)	0.835
10^9 cells.l^{-1}	81.2 (65.0 - 101.4)	84.1 (66.2 - 106.9)	
Maximum reticulocyte index first 7 days			
log	0.95 (0.43)	0.93 (0.35)	0.835
%	2.59 (2.01 - 3.34)	2.54 (2.06 - 3.13)	
STRC final day	17.4 (14.5 - 18.2) [10.1 - 23.1]	15.5 (12.1 - 18.2) [9.3 - 21]	0.607
Total transfusions during admission	2 (2 - 2.5) [1 - 4]	2 (2 - 2.5) [1 - 4]	1.000
Total transfusions in first week	2 (2 - 2) [1 - 4]	2 (2 - 2.5) [1 - 4]	0.882

Data are reported as mean (sd), median (interquartile range) [range], or number (proportion). The mean (sd) for log transformed data are supplemented by the back-transformed mean (95% confidence interval). P values are from: two-side tests on the log-transformed data; chi-squared tests with continuity correction; and Mann-Whitney-U tests on non-parametric data.

Table 2C

Haematological outcomes for non-transfused participants

	Control (n = 30)	Iron (n = 28)	p
Reticulocytes final day	(n = 26)	(n = 24)	
log	4.23 (0.38)	4.56 (0.33)	0.002
10^9 cells.l^{-1}	68.9 (59.6 – 79.6)	95.3 (83.3 - 108.9)	
Reticulocytes day 7	(n = 22)	(n = 20)	
log	4.31 (0.34)	4.56 (0.33)	0.015
10^9 cells.l^{-1}	74.2 (64.4 - 85.3)	95.7 (82.7 - 110.7)	
Reticulocyte index final day	(n = 26)	(n = 24)	
log	0.75 (0.40)	1.05 (0.33)	0.002
%	2.01 (1.72 - 2.35)	2.86 (2.5 - 3.26)	
Reticulocyte index day 7	(n = 22)	(n = 20)	
log	0.76 (0.39)	1.04 (0.32)	0.015
%	2.13 (1.82 - 2.5)	2.82 (2.45 - 3.24)	
Haemoglobin final day	(n = 27)	(n = 25)	
log	4.62 (0.14)	4.63 (0.11)	0.871
g.l^{-1}	102.0 (96.7 - 107.5)	102.2 (98.1 - 106.6)	
Haemoglobin day 7	(n = 24)	(n = 20)	
log	4.64 (0.14)	4.64 (0.10)	0.988
g.l^{-1}	103.9 (98.4 - 109.8)	104.0 (99.7 - 108.5)	
Minimum haemoglobin first 7 days			
log	4.55 (0.12)	4.57 (0.11)	0.475
g.l^{-1}	94.9 (90.9 - 99.0)	97.0 (93.0 - 101.2)	
Maximum fall in haemoglobin first 7 days			
log	3.40 (0.41)	3.33 (0.58)	0.676
g.l^{-1}	30.0 (25.9 - 34.7)	27.9 (22.4 - 34.7)	
Maximum reticulocytes first 7 days			
log	4.25 (0.32)	4.51 (0.35)	0.004
10^9 cells.l^{-1}	69.8 (62.2 – 78.2)	90.7 (79.8 - 103.2)	
Maximum reticulocyte index first 7 days			
log	0.70 (0.38)	0.98 (0.37)	0.006
%	2.01 (1.76 - 2.30)	2.66 (2.32 - 3.05)	
STRC final day	17.5 (14.8 - 19.2) [11.4 - 24.8]	16.1 (14.9 - 17.6) [9.6 - 24.8]	0.522
Total transfusions during admission	0 (0 - 0) [0 - 2]	0 (0 - 0) [0 - 0]	1.000
Participants transfused during admission	1 (3)	0	1.000

Table 2D

Haematological outcomes for participants admitted with haemoglobin < 120 $g.l^{-1}$

	Control (n = 15)	Iron (n = 16)	p
Reticulocytes final day		(n = 15)	
log	4.12 (0.40)	4.31 (0.34)	0.160
10^9 cells.l^{-1}	61.3 (49.7 - 75.6)	74.8 (62.9 – 89.0)	
Reticulocytes day 7	(n = 10)	(n = 11)	
log	4.16 (0.34)	4.28 (0.27)	0.387
10^9 cells.l^{-1}	64.2 (52.4 - 78.7)	72.2 (61.4 - 84.8)	
Reticulocyte index final day		(n = 15)	
log	0.68 (0.46)	0.85 (0.34)	0.259
%	1.96 (1.55 - 2.50)	2.33 (1.96 - 2.78)	
Reticulocyte index day 7	(n = 10)	(n = 11)	
log	0.76 (0.43)	0.81 (0.23)	0.717
%	2.13 (1.64 - 2.78)	2.25 (1.96 - 2.58)	
Haemoglobin final day		(n = 15)	
log	4.54 (0.11)	4.58 (0.09)	0.212
$g.l^{-1}$	93.4 (88.0 - 99.1)	97.9 (93.7 - 102.2)	
Haemoglobin day 7	(n = 12)	(n = 11)	
log	4.53 (0.11)	4.60 (0.07)	0.050
$g.l^{-1}$	92.3 (86.9 - 98.1)	100.0 (95.9 - 104.2)	
Minimum haemoglobin first 7 days			
log	4.45 (0.16)	4.43 (0.11)	0.688
$g.l^{-1}$	85.5 (78.9 - 92.8)	83.9 (79.4 - 88.6)	
Maximum fall in haemoglobin first 7 days			
log	3.13 (0.90)	2.74 (0.88)	0.240
$g.l^{-1}$	22.8 (14.5 - 36.1)	15.5 (10.1 - 23.9)	
Maximum reticulocytes first 7 days			
log	4.15 (0.32)	4.38 (0.31)	0.053
10^9 cells.l^{-1}	63.7 (54.1 - 74.9)	80.1 (68.7 - 93.4)	
Maximum reticulocyte index first 7 days			
log	0.67 (0.43)	0.90 (0.31)	0.109
%	1.96 (1.58 - 2.44)	2.45 (2.1 - 2.86)	
STRC final day	15.8 (14.3 - 17.9) [10.1 - 23]	15.4 (14 - 18.2) [11.4 - 24.8]	1.000
Total transfusions during admission	0 (0 - 2) [0 - 4]	0.5 (0 - 2) [0 - 4]	1.000
Participants transfused during admission	7 (47)	8 (50)	1.000
Total transfusion during first 7 days	0 (0 - 2) [0 - 4]	0.5 (0 - 2) [0 - 4]	0.710
Participants transfused during first 7 days	6 (40)	8 (50)	0.843

Table 2E

Haematological outcomes for participants with intracapsular fractures

	Control (n= 24)	Iron (n = 26)	p
Reticulocytes final day	(n = 20)	(n = 23)	
log	4.17 (0.34)	4.36 (0.31)	0.053
10^9 cells.l^{-1}	64.4 (55.5 – 74.7)	78.4 (69.1 – 88.9)	
Reticulocytes day 7	(n = 16)	(n = 20)	
log	4.24 (0.30)	4.41 (0.28)	0.090
10^9 cells.l^{-1}	69.1 (59.7 – 80.0)	81.9 (72.4 - 92.8)	
Reticulocyte index final day	(n = 20)	(n = 23)	
log	0.60 (0.35)	0.87 (0.28)	0.008
%	1.82 (1.56 - 2.13)	2.38 (2.13 - 2.67)	
Reticulocyte index day 7	(n = 16)	(n = 20)	
log	0.65 (0.33)	0.91 (0.25)	0.012
%	1.91 (1.62 - 2.25)	2.47 (2.22 - 2.76)	
Haemoglobin final day	(n = 21)	(n = 23)	
log	4.65 (0.13)	4.63 (0.10)	0.506
g.l^{-1}	105 (99.4 - 111)	102.6 (98.3 - 107.1)	
Haemoglobin day 7	(n = 18)	(n = 20)	
log	4.68 (0.11)	4.64 (0.10)	0.224
g.l^{-1}	108.2 (102.8 - 113.9)	103.7 (99.1 - 108.5)	
Minimum haemoglobin first 7 days			
log	4.59 (0.12)	4.56 (0.14)	0.432
g.l^{-1}	98.1 (93.6 - 102.7)	95.3 (90.3 - 100.5)	
Maximum fall in haemoglobin first 7 days			
log	3.29 (0.42)	3.23 (0.60)	0.678
g.l^{-1}	26.8 (22.7 - 31.7)	25.2 (20.1 - 31.7)	
Maximum reticulocytes first 7 days			
log	4.17 (0.31)	4.37 (0.29))	0.019
10^9 cells.l^{-1}	64.6 (57.1 – 73.0)	79.3 (70.9 - 88.7)	
Maximum reticulocyte index first 7 days			
log	0.59 (0.34)	0.85 (0.29))	0.005
%	1.80 (1.57 - 2.06)	2.34 (2.09 - 2.62)	
STRC final day	16.5 (13.9 - 18.4) [11.4 - 23.1]	16 (14.1 - 16.4) [9.6 - 21]	0.415
Total transfusions during admission	0 (0 - 0) [0 - 2]	0 (0 - 0.8) [0 - 4]	0.173
Participants transfused during admission	3 (12.5)	7 (26.9)	0.358
Total transfusions in first week	0 (0 - 0) [0 - 1]	0 (0 - 0.8) [0 - 4]	0.050
Participants transfused during first week	1 (4)	4 (15)	0.396

Table 2F

Haematological outcomes for participants with extracapsular fractures

	Control (n = 17)	Iron (n = 13)	p
Reticulocytes final day			0.031
log	4.41 (0.39)	4.74 (0.38)	
10^9 cells.l^{-1}	82.5 (68.6 - 99.2)	115 (92.6 - 142.8)	
Reticulocytes day 7	(n = 14)	(n = 9)	0.090
log	4.43 (0.42)	4.75 (0.43)	
10^9 cells.l^{-1}	84.2 (67.7 - 104.6)	115.8 (87.4 - 153.5)	
Reticulocyte index final day			0.117
log	0.98 (0.42)	1.22 (0.37)	
%	2.66 (2.19 - 3.24)	3.4 (2.75 - 4.2)	
Reticulocyte index day 7	(n = 14)	(n = 9)	0.269
log	1.02 (0.43)	1.22 (0.39)	
%	2.78 (2.22 - 3.48)	3.4 (2.63 - 4.38)	
Haemoglobin final day			0.062
log	4.54 (0.11)	4.61 (0.09)	
$g.l^{-1}$	93.5 (88.6 - 98.7)	100.8 (95.8 - 106.1)	
Haemoglobin day 7	(n = 15)	(n = 9)	0.024
log	4.53 (0.11)	4.63 (0.07)	
$g.l^{-1}$	92.4 (87.4 - 97.6)	102.1 (97.2 - 107.2)	
Minimum haemoglobin first 7 days			0.274
log	4.39 (0.16)	4.45 (0.13)	
$g.l^{-1}$	81.0 (75.1 - 87.3)	85.9 (80.2 - 92.1)	
Maximum fall in haemoglobin first 7 days			0.506
log	3.52 (0.96)	3.28 (0.99)	
$g.l^{-1}$	33.8 (21.4 - 53.4)	26.6 (15.5 - 45.5)	
Maximum reticulocytes first 7 days			0.053
log	4.45 (0.32)	4.71 (0.39)	
10^9 cells.l^{-1}	85.8 (73.9 - 99.7)	111.4 (90 - 137.9)	
Maximum reticulocyte index first 7 days			0.195
log	1.02 (0.35)	1.20 (0.38)	
%	2.79 (2.36 - 3.28)	3.32 (2.71 - 4.07)	
STRC final day	(n = 13)	(n = 6)	0.726
	17.7 (15.8 - 19) [10.1 - 24.8]	19.2 (13.6 - 23.2) [9.3 - 24.8]	
Total transfusions during admission	2 (0 - 2) [0 - 4]	0 (0 - 2) [0 - 4]	0.314
Participants transfused during admission	9 (53)	4 (31)	0.399
Total transfusions in first week	2 (0 - 2) [0 - 4]	0 (0 - 2) [0 - 4]	0.293
Participants transfused during first week	9 (53)	4 (31)	0.399

FUNCTIONAL AND SAFETY OUTCOMES

Table 3:

Secondary safety outcomes

	Control (n = 41)	Iron (n = 39)	p
Infective complications	12 (29)	8 (21)	0.518
Cardiovascular complications	10 (24)	9 (23)	1.000
Cumulated ambulation score	43.5 (24 - 56) [8 - 82]	32 (19.2 - 48) [0 - 85]	0.137
Length of hospital stay			
log	2.66 (0.45)	2.60 (0.54)	0.605
days	14.2 (12.4 - 16.4)	13.4 (11.4 - 15.9)	
Length of postoperative hospital stay			
log	2.56 (0.48)	2.48 (0.59)	0.527
days	12.9 (11.1 - 15)	12 (9.9 - 14.4)	
Discharge destination			0.349
Died	0	3 (8)	
Nursing Home	1 (2)	2 (5)	
Own Home	27 (66)	25 (64)	
Rehab hospital	11 (27)	7 (18)	
Residential Home	1 (2)	2 (5)	
Warden controlled accommodation	1 (2)	0	
Mortality at 30-days	0	4 (10)	0.112

Data are reported as mean (sd), median (interquartile range) [range], or number (proportion). The mean (sd) for log transformed data are supplemented by the back-transformed mean (95% confidence interval). P values are from: two-side tests on the log-transformed data; chi-squared tests with continuity correction; and Mann-Whitney-U tests on non-parametric data.