

BMJ Open The UK Cardiac and Vascular Surgery Interventional Anaemia Response (CAVIAR) Study: protocol for an observational cohort study to determine the impact and effect of preoperative anaemia management in cardiac and vascular surgical patients

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ABSTRACT

Introduction Preoperative anaemia is linked to poor postsurgical outcome, longer hospital stays, greater risk of complications and mortality. Currently in the UK, some sites have developed anaemia clinics or pathways that use intravenous iron to correct iron deficiency anaemia prior to surgery as their standard of care. Although intravenous iron has been observed to be effective in a variety of patient settings, there is insufficient evidence in its use in cardiac and vascular patients. The aim of this study is to observe the impact and effect of anaemia and its management in patients undergoing cardiac and vascular surgery. In addition, the UK Cardiac and Vascular Surgery Interventional Anaemia Response (CAVIAR) Study is also a feasibility study with the aim to establish anaemia management pathways in the preoperative setting to inform the design of future randomised controlled trials.

Methods and analysis The UK CAVIAR Study is a multicentre, stepped, observational study, in patients awaiting major cardiac or vascular surgery. We will be examining different haematological variables (especially hepcidin), functional capacity and patient outcome. Patients will be compared based on their anaemia status, whether they received intravenous iron in accordance to their hospital's preoperative pathway, and their disease group. The primary outcomes are the change in haemoglobin levels from baseline (before treatment) to before surgery; and the number of successful patients recruited and consented (feasibility). The secondary outcomes will include changes in biomarkers of iron deficiency, length of stay, quality of life and postoperative recovery.

Ethics and dissemination The study protocol was approved by the London-Westminster Research Ethics Committee (15/LO/1569, 27 November 2015). NHS approval was also obtained with each hospital trust. The findings of the study will be published in peer-reviewed journals.

Trial registration number Clinical Trials registry (NCT02637102) and the ISRCTN registry (ISRCTN55032357).

Strengths and limitations of this study

- This is the first study examining how iron treatment and major surgery affects haematological variables, functional capacity and patient outcome.
- Furthermore, this study will also be the first to compare cardiac with vascular patient groups.
- The results of this study will provide information in the understanding of preoperative anaemia, and whether correcting iron deficiency anaemia will lead to improved surgical outcomes.
- Slight variations in preoperative anaemia pathways used in different hospitals.
- Different intravenous iron will be used in different hospitals.

INTRODUCTION

There is increasing evidence that preoperative anaemia is associated with a higher risk of complications, prolonged hospital stay, transfusion requirement and mortality.^{1–5} Anaemia is becoming increasingly prevalent largely due to an ageing population. The estimated prevalence of anaemia is up to 50% of patients in some hospitals.⁶ There is also considerable variability in prevalence in different hospitals and regions of the UK.⁷ Nutritional deficiencies of iron, folate and/or vitamin B₁₂ contribute to approximately a third of the cases preoperatively, whereas functional iron deficiency (FID) or iron restriction appears to be more common but its relevance is less well understood.⁸

FID exists when there is failure of the bioavailability of iron for erythropoiesis. The mechanism occurs via inflammatory

mediators induced by pre-existing illness or comorbid disease. Hepcidin, an important regulator of iron homeostasis, is upregulated under inflammatory conditions⁹ and prevents export of iron from cells. This results in the increased uptake and retention of iron from the circulation by the reticular endothelial system, thus reducing bioavailability of iron for erythropoiesis.¹⁰ A retrospective study by Hung and colleagues⁸ demonstrated an association of elevated hepcidin with poorer outcome in cardiac patients. Therefore strategies in correcting and managing FID may play a vital role in improving postsurgical outcomes.

Intravenous iron has been shown to be an effective treatment of anaemia in a variety of settings, including heart failure, inflammatory bowel disease and orthopaedic surgery.¹¹⁻¹⁴ The Cochrane review by Gurusamy and colleagues¹⁵ examined the effectiveness of different iron therapies in patients with anaemia and concluded that due to significant heterogeneity and low quality of the trials reviewed, there were insufficient grounds to support the role of treating patients with intravenous iron preoperatively. The updated review however showed increased efficacy of intravenous iron in correcting haemoglobin levels (Hb)¹⁶ as well as treatment with intravenous iron showed improvement in symptoms, exercise capacity and quality of life, typically in patients with heart failure.¹¹⁻¹⁴ There is still insufficient evidence for the effectiveness it may have in cardiac patients.¹⁷

National guidelines have recommended that anaemia should be identified before surgery and treated if appropriate.¹⁸ In the UK, a number of centres have introduced anaemia clinics or developed preoperative anaemia pathways incorporating intravenous iron as part of their standard of care. As the current evidence for different iron therapies is limited and variation exists, it is important to understand how these treatments given preoperatively may affect patient fitness for surgery and outcomes.

In light of this, we have designed a study to observe the impact and effect of anaemia and its management in patients undergoing cardiac and vascular surgery. We also aim to assess the regional variations in preoperative pathways, patients' outcomes postoperatively and their requirement for transfusion. In addition, this study aims to gather information about the feasibility of establishing anaemia management pathways in the preoperative setting to guide the design of future randomised controlled trials (RCTs).

METHODS AND ANALYSIS

This study is a multicentre, stepped, prospective, observational platform comprising two cohorts in patients awaiting major cardiac or vascular surgery. In the first cohort we will examine the effect of anaemia and outcomes (cohort 1), and in the second cohort we will assess the effect of treatment of anaemia (cohort 2) in both population groups. The study is stepped, whereby cohort 1 will initially be identified on the day of surgery and then

following feasibility at least 10 days before operation. This enables a step to cohort 2 as the sites can feasibly identify and recruit patients in the appropriate time frame. The advantage of this is that the study can examine a number of outcome variables, and will permit calculation of the effect of each variable on the probability of developing the outcome of interest (relative risk) (please see online supplementary file for the STROBE checklist).¹⁹

Patients will be identified through routine clinical care, which, depending on the participating site, may include surgical outpatients, preadmission clinics, or referral for cardiopulmonary exercise test (CPET) or 6 min walk test (6MWT) prior to their planned surgery. Local clinicians or research nurses will screen scheduled elective surgery lists and their haemoglobin blood results (within the last 3 months) for eligible patients. Frequency of the screening and contact with the patient has been left to the discretion of the local staff as time and resources vary between hospitals. In addition, each site will be requested to recruit patients in a consecutive manner. The study therefore acts to be a feasibility assessment of local teams to identify patients for preoperative clinical trials.

Anaemia in this study satisfies WHO criteria with (Hb) <130 g/L in men and <120 g/L in women.²⁰⁻²¹

Inclusion criteria are: patients aged 18 years or over, undergoing elective cardiac or vascular surgery (eg, coronary artery bypass graft (CABG), valve surgery, repair or replacement of thoracic or abdominal aorta (open or endovascular), revascularisation or endarterectomy), with written informed consent.

Exclusion criteria are: patients who are pregnant or lactating, undergoing renal dialysis (current or planned within the next 12 months), prisoners and patients who have an underlying history of learning disabilities or adults who do not have mental capacity to consent for themselves.

Recruited patients will then be categorised as below (see [figure 1](#)).

1. Patients prior to major cardiac or vascular surgery, in whom consent is taken before operation
2. Patients prior to major cardiac or vascular surgery, in whom consent is taken at least 10 or more days before operation
3. Patients prior to major cardiac or vascular surgery, in whom consent is taken at least 10 or more days before operation in whom a functional exercise assessment is performed (CPET or 6MWT)

Substudy arm

In patients who receive intravenous iron as part of normal clinical practice at that hospital:

1. Patients who have consented for blood sampling (ie, additional core blood samples) before and after intravenous iron
2. Patients who have consented for blood sampling and in addition in whom a functional exercise assessment is performed (CPET or 6MWT) before and after intravenous iron

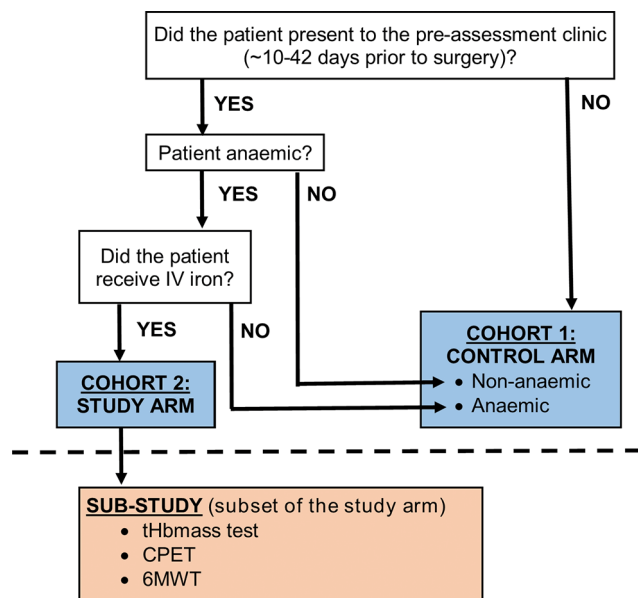


Figure 1 Patient categorisation. 6MWT, 6 mins walk test; CPET, cardiopulmonary exercise test; IV, intravenous; tHbmass, total haemoglobin mass.

3. Patients who have consented for blood sampling and in addition in whom a total haemoglobin mass (tHbmass) test is performed before and after intravenous iron

Assessments

Patient data will be obtained from medical records and will be used to assess the approach to anaemia management between the participating sites. Information will include patients' past medical history, medications, bloods (including haematinics, ferritin and C reactive protein), CPET or 6MWT (if applicable), quantity of blood transfused, length of intensive care unit (ICU) and hospital stay and complications relating to index surgery. Data will be collected from consent to prospectively during hospital admission, up until 4–6 weeks at routine clinic follow-up appointment.

In addition to the routine medical information, the trial will also request additional assessments (see online supplementary file 1). These include:

1. Additional core blood tests to examine iron status, hepcidin and serum proteins;
2. Health-related Quality of life (HRQoL) questionnaires (comprised of Single Question Outcome Measure, Multidimensional Fatigue Inventory and EuroQol in the study arm only);
3. Days alive and out of hospital (DAOH) at follow-up for all arms (at 30 days postsurgery), calculated as per Ariti and colleagues.^{8 22}

Substudy only:

1. If CPET/6MWT was done routinely at baseline before iron therapy (eg, preassessment clinic), we would ask the patient to repeat the same test after iron therapy. Both CPET and 6MWT will be included in this study. CPET is an objective

measure in determining response of patients who undergo major surgery through quantifying oxygen consumption and carbon dioxide production.²³ Although it is considered the gold standard assessment of functional capacity, it is however not routinely used in all NHS hospitals. The alternative option is the 6MWT, which is easy to administer and does not require special equipment, and involves walking up and down a 100 ft hallway. The limitation to the 6MWT is that it is only a good indicator for daily activities and not so much on peak oxygen uptake.²⁴

2. Selected sites will conduct the tHbmass test (as this requires special equipment and training) using the optimised carbon monoxide rebreathing method²⁵ before and after iron therapy. tHbmass represents absolute mass of circulating haemoglobin and has been suggested to be a more reliable marker in determining oxygen carrying capacity and in predicting postsurgical outcome compared with using Hb or blood volume alone.²⁶ The test involves breathing through a tube that is attached to a bag containing small amounts of carbon monoxide for 2 min. Blood samples will be taken from the fingertip or earlobe before and after carbon monoxide exposure to determine carboxyhaemoglobin concentration.²⁵ This will be exploratory in nature to determine the feasibility and practicality if carried out in a 'hospital' setting.

Where possible, assessments will coincide with routine hospital schedules and clinical blood tests. All data will be entered by local staff into a password-protected, electronic case report form (eCRF). Any missing data will be noted in the eCRF. All information collected will be kept confidential and in accordance with the UK Data Protection Act 1998. **Figure 2** shows the flow chart of the UK Cardiac and Vascular Surgery Interventional Anaemia Response (CAVIAR) Study.

Patient outcome measures

The primary outcomes for this study are:

- ▶ Change in Hb from baseline (before treatment) to before surgery in the study arm; and
- ▶ The number of successful patients recruited and consented (feasibility).

The secondary outcomes are:

- ▶ Change in Hb from before treatment to postsurgery;
- ▶ Changes in biomarkers of iron deficiency (eg, hepcidin, ferritin, transferrin saturation) from before and after iron therapy;
- ▶ Units of blood transfused perioperatively; length of stay (LOS) in hospital and ICU;
- ▶ Renal function (change in creatinine) from baseline to before or after surgery; complications during hospital stay;
- ▶ HRQoL questionnaires before and after iron therapy (or after surgery for substudy).

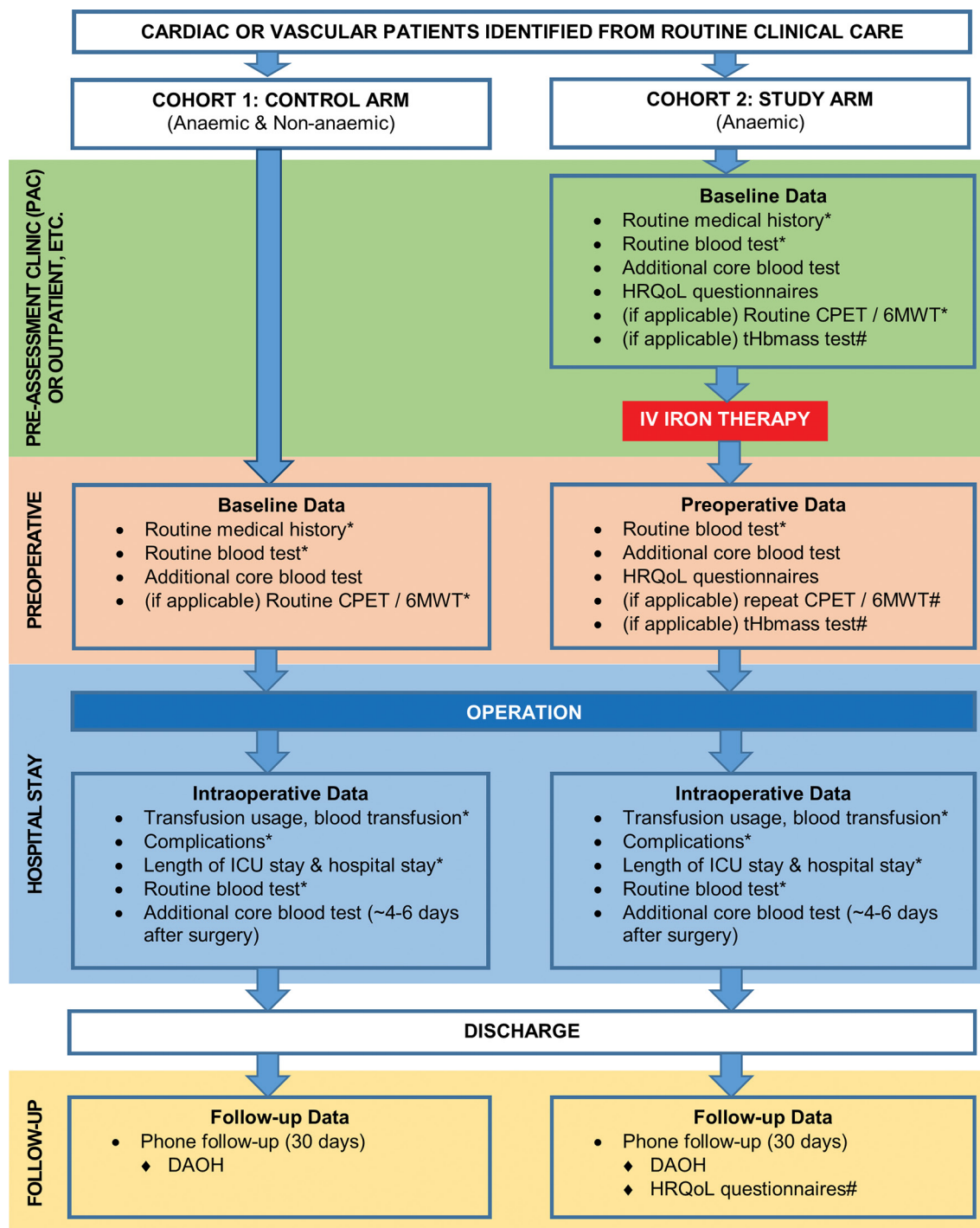


Figure 2 Flow chart of the UK CAVIAR Study. * Collected from patient's medical records. # Only relevant for the substudy arm. CAVIAR, Cardiac and Vascular Surgery Interventional Anaemia Response; 6MWT, 6 min walking test; CPET, cardiopulmonary exercise test; DAOH, days alive and out of hospital; HRQoL, health-related quality of life; ICU, intensive care unit; IV, intravenous; tHbmass, total haemoglobin mass.

► For the substudy only arm: CPET/6MWT before and after iron therapy; and tHbMass test before and after iron therapy.

Sample size calculation

The sample size was calculated for the primary end point of change in Hb from baseline to 10–42 days before surgery for those who receive intravenous iron. Assuming that the SD for Hb will be 12g/L,^{7 27}

72 patients will provide 90% power at the 5% significance level (allowing for up to 10% loss to follow-up) to demonstrate a difference in the change from baseline in Hb of 10g/L. We will therefore recruit 72 cardiac surgery patients and 72 vascular surgery patients for the study arm (cohort 2). In patients who received intravenous iron in the study arm, an arbitrary number of 12 from each of the patient groups will be asked to participate in the substudy arm. This substudy arm will be



exploratory in nature, used to determine the feasibility and practicality to carry these additional assessments in a 'hospital setting'.

For the control arm, we will recruit patients who are anaemic and non-anaemic (cohort 1). Controls will be collected sequentially for the duration of the trial to avoid time bias and sampling error. Therefore, control patients will be recruited at twice the number than the study group. Overall, a total of 432 patients will be recruited to this study. See online supplementary file 2 for the number of patients per group.

Statistical analysis

Baseline demographics of the patients will be described using summary statistics. Continuous variables will be summarised using the mean and SD if approximately normally distributed. Continuous variables that are not normally distributed will be summarised using the median and IQR. Differences between groups will be assessed using two-sample t-tests for normally distributed variables. For variables that are not normally distributed an appropriate transformation will be carried out followed by a two-sample t-test. If no appropriate transformation can be found a non-parametrical test will be used. Categorical variables will be described using frequency and percentage and differences between groups will be tested using χ^2 or Fisher's exact tests as appropriate. The linear association between tHbmass, maximal oxygen consumption ($\dot{V}O_2$) and iron indices will be evaluated using Pearson correlation coefficient and linear regression. Adjusted analyses will be carried out using multivariable linear regression. The accuracy of the subsequent model for outcome predictions will be determined using a receiver operating characteristic (ROC) curve analysis. Depending on the distribution of the data, linear regression (with a log transformation), Poisson or negative binomial model will be used to assess the value of preoperative tHbmass as a predictor of the primary outcome, postoperative morbidity and secondary outcome variables (hospital LOS, ICU LOS).

DISCUSSION

Preoperative anaemia is recognised in cardiac and vascular surgery. Anaemia is linked independently with worse outcome, including length of hospital stay and mortality. Despite studies having shown that intravenous iron is effective in a variety of population groups,^{11–14} there is still insufficient evidence to support its use. The current published evidence is of low quality or too heterogeneous.¹⁵ Furthermore, to our knowledge there are no RCTs that have been conducted looking at iron therapy in cardiovascular patients.

The UK CAVIAR Study is an observational, multi-centre trial, to investigate the impact of anaemia and its management in cardiovascular patients, and the feasibility to study patients in the platform for a future planned RCT.

There is currently limited information on how iron treatment and major surgery have an influence on haematological parameters, functional parameters and patient outcome in cardiovascular patients. Hepcidin, a key regulator of iron homeostasis⁹ was observed to be the only haematological variable that was associated with worse outcome in cardiac patients; and that nearly half of the patients identified had FID.⁸ Other studies that examined healthy participants and athletes with or without anaemia and iron deficiency had reduced functional capacity.^{28–30} It is therefore reasonable to assume that patients may respond to iron treatment, and may lead to improved outcomes. Our study is the first study to examine these areas and aims to provide insight on how intravenous iron and major surgery may influence hepcidin and other haematological variables, functional capacity and outcomes in cardiovascular patients. In addition, this study will also be the first to compare these two different, yet similar, population groups; and their outcomes assessed through using a composite of mortality and LOS in hospital (ie, DAOH).

One of the outcomes assessed in this study is patient DAOH at 30 days postsurgery. Traditionally in clinical trials, mortality and morbidity are often used as end point to determine treatment efficacy, however, it does not take into account the frequency for readmission, duration and severity. The DAOH is a composite score and is based on varying weightings placed on mortality and readmission factors, and therefore provides a clearer summary on the overall treatment effect.²²

In our substudy, we are exploring tHbmass as an alternative marker in determining oxygen carrying capacity and in predicting postsurgical outcome. The insult of surgery puts enormous metabolic stress on the body and thereby an increase in the demand for oxygen is seen as a result. The inability to deliver enough oxygen to where it is needed may increase the risk of having poorer surgical outcomes.^{31 32} tHbmass represents absolute mass of circulating Hb and is relatively unexplored in the clinical setting, particularly in cardiovascular patients. Although Hb is traditionally used, studies have shown that Hb may not be a reliable or accurate measure as it can be influenced by fluid shifts (eg, blood loss) or haemodilution, which is commonly observed in ICU.^{26 33} If tHbmass provides a stronger link over Hb in predicting postsurgical outcome, this will be a useful measure in determining which and when patients can go into surgery; and can also be a target in raising tHbmass to improve outcome.

One of the key hurdles we anticipate in this study is the identification and recruitment of patients in the intravenous iron arm 10–42 days prior to surgery. The timeframe required is to allow at least 10 days for the intravenous iron to have an effect of increasing Hb. As resources and infrastructure will vary between hospitals, this feasibility study will therefore help build the framework in setting up a preoperative anaemia pathway, and to best identify and manage these patients.

Correcting anaemia preoperatively is recognised as an integral part of patient blood management by the NHS. Blood use in cardiac patients has been shown to increase every year,³⁴ while vascular patients on average receive 2–3 units of blood during their hospital stay.³⁵ The cost of transfusing a single unit of blood has been estimated to be £170 for the first unit, with the subsequent unit costing £162. If the number of units of blood used is reduced, there will be a potential saving of £146–689 per person.³⁶ Apart from the cost-saving, the reduction in blood transfused in patients will reduce the likelihood of the associated worse outcomes that are often observed. These include postoperative infection and longer hospital stay.³⁷ More importantly, for patients, correcting anaemia could significantly improve their outcome and quality of life as observed in patients with heart failure.^{11 14}

The ultimate goal for this and the future RCTs is to have a preoperative anaemia pathway in place in every hospital so that patients with anaemia are identified early and corrected prior to surgery.

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Contributors TR and AK are the chief investigators, protocol authors and grant holders. MC is the manager for the trial and has drafted this manuscript. CE assisted in the design of the study and helped draft the manuscript. AB assisted in drafting the manuscript. TC participated in the statistical design of the study. All authors read and approved the final manuscript.

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Competing interests MC's salary is supported by Pharmacosmos A/S. TR reports grants from NIHR HTA (UK); grants from NHMRC (Australia); grants from NIAA / BJA / ACTA / VASGBI (UK); grants, personal fees and non-financial support from Pharmacosmos; grants, personal fees and non-financial support from Vifor Pharma; grants, personal fees and non-financial support from Acelyt; grants, personal fees and non-financial support from Stroke Association; grants from Mason Medical Research Foundation; grants from UCH League of Friends; grants and non-financial support from Libresse/ Bodyform; outside the submitted work. TR is a regular speaker at national and international conferences on anaemia, blood transfusion, wound healing and vascular diseases for which he has received expenses for travel, accommodation and sundries. TR is the Director of The IronClinic Ltd, Director of Veincare London Ltd, and is also the Vascular lead for 18-week wait Ltd. CE is a Consultant for Pharmacosmos. AK has received research funding and honoraria from Pharmacosmos, Vifor Pharma, CSL Behring and Brightwake Ltd. AK is the Editor-in-Chief of Anaesthesia. There is no external or industry involvement in CAVIAR.

Ethics approval London Westminster Research Ethics Committee.

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