Transfusion after acute upper gastrointestinal haemorrhage

Published Online
May 6, 2015
http://dx.doi.org/10.1016/S0140-6736(14)62351-5

See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(14)61999-1

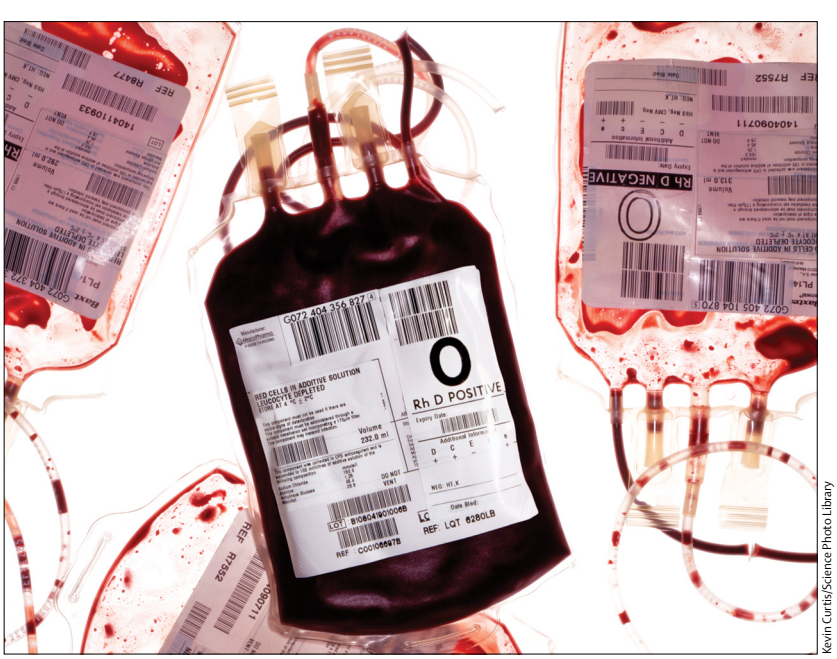
In *The Lancet*, Vipul Jairath and colleagues[1] report on a feasibility trial of restrictive versus liberal blood transfusion in acute upper gastrointestinal haemorrhage. Six UK hospitals were randomly assigned to either a restrictive (transfusion when haemoglobin concentration fell below 80 g/L; 403 patients enrolled) or liberal (transfusion when haemoglobin concentration fell below 100 g/L; 533 patients enrolled) red blood cell transfusion policy for patients with acute upper gastrointestinal bleeding. Several feasibility outcomes were investigated, and the number of units of red blood cells that were transfused in patients according to the restrictive policy as compared with the liberal policy was non-significantly reduced (mean number of units 1·2 [SD 2·1] *vs* 1·9 [2·8]; difference –0·7 [95% CI –1·6 to 0·3]). The question of which policy to use is important, and the answer could have an effect on outcomes and economics of treatment, although the results of this trial should not be used to inform changes in present guidance, but should be viewed as an important precursor to a large randomised controlled trial.

The role of blood transfusion in non-exsanguinating haemorrhage from the gastrointestinal tract is controversial, and evidence exists of substantial variation in practice.[2,3] Large observational studies[4] that have been used to create and validate risk assessment methods have shown that haemoglobin concentration is not an independent prognostic factor in multivariate analysis, and does not feature in the resulting scoring system. Investigators of a few studies with varying levels of evidence have concluded that a restrictive policy and low trigger threshold for transfusion is beneficial, and that even if no absolute clinical advantage of a restrictive practice exists, then, as long as this is not detrimental, avoidance of blood transfusion in an increased proportion of patients both reduces transfusion risk and is economically beneficial.

Important publications in 2013 seemed to favour a restrictive policy,[5,6] but, as pointed out by Jairath and colleagues,[1] both the case-mix and exclusions in the only existing sufficiently powered randomised controlled trial, done in Barcelona, Spain,[6] make generalisation of the conclusions difficult. The very rapid access to interventional endoscopy in this Barcelona trial is not replicated in most hospitals in the UK, and this access in itself could affect transfusion. The proportion of patients with liver disease was much higher in the Barcelona study than the UK generally, and patients with major cardiovascular comorbidity were excluded. One of the recruitment discrepancies in Jairath and colleagues' feasibility trial was the proportion of patients with liver disease at each site, and this discrepancy is likely to be due to the specialist services provided within the clusters. Patients with liver disease who bleed could be argued to form a very different subgroup to those without liver disease and might reasonably be excluded from a future trial, and, in any case, only represent about 10% of all bleeds in the UK.

To obtain systematic evidence of an appropriate transfusion trigger after acute upper gastrointestinal haemorrhage is therefore a worthy aim. Jairath and colleagues' trial[1] has achieved good case ascertainment and protocol adherence, and identified areas of the protocol that could be adjusted to improve a future trial. A problem such as reduced protocol adherence in the liberal group is likely to be at least partly corrected by exclusion of the lowest-risk patients.

The benefit of blood transfusion in stable patients is difficult to assess. Many studies outside the context of gastrointestinal haemorrhage have been done, such as in trauma,[7] critical care,[8] cardiac surgery,[9] and hip surgery,[10]



Kevin Curtis/Science Photo Library

that describe either worse outcomes in transfused patients or no advantage in the liberally transfused group compared with the restrictive group.[11] Transfused blood has some well known risks, and is not entirely effective at replacing all normal blood functions. Sound physiological reasons also exist for why reduction of a transfusion trigger should be considered.[12] Replacement of blood in the anaemic patient aims to increase oxygen delivery, but oxygen delivery to tissues is not dependent on a normal haemoglobin concentration once normovolaemia has been restored. Oxygen delivery is dependent on cardiac output and oxygen extraction, both of which are increased by a reduction in blood viscosity (a consequence of anaemia) that leads directly to redistribution of blood flow, allowing increased oxygen extraction and ventricular performance. In fact, oxygen delivery only starts to fall when haematocrit is less than 25%, which equates to a haemoglobin concentration of about 80 g/L.[12] Even then, oxygen delivery is substantially greater than demand, so this demand can still be met well below this haemoglobin concentration. Therefore, in the non-exsanguinating case of most gastrointestinal bleeds, blood transfusion might not affect the main aim of increased oxygen delivery.

Guidelines on transfusion after acute upper gastrointestinal haemorrhage vary in their recommendations. A criticism of guidelines generally is that, by necessity, they are often based more on opinion than fact. If guidelines on this subject are to be updated in the future, then the proposed trial will hopefully provide the data on which to formulate solid guidance. A large, well run, pragmatic trial is to be welcomed.

Timothy A Rockall
Royal Surrey County Hospital NHS Trust, Guildford, Surrey GU2 7XX, UK
tim.rockall@btinternet.com

I declare no competing interests.

1 Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. *Lancet* 2015; published online May 6. http://dx.doi.org/10.1016/S0140-6736(14)61999-1.
2 Jairath V, Kahan BC, Logan RF, Travis SP, Palmer KR, Murphy MF. Red blood cell transfusion practice in patients presenting with acute upper gastrointestinal bleeding: a survey of 815 UK clinicians. *Transfusion* 2011; **51:** 1940–48.
3 Jairath V, Hearnshaw S, Brunskill SJ, et al. Red cell transfusion for the management of upper gastrointestinal haemorrhage. *Cochrane Database Syst Rev* 2010; **9:** CD006613.
4 Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996; **38:** 316–21.
5 Al-Jaghbeer M, Yende S. Blood transfusion for upper gastrointestinal bleeding: is less more again? *Crit Care* 2013; **17:** 325.
6 Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; **368:** 11–21.
7 Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma* 2003; **54:** 898–905.
8 Herbert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled trial of transfusion requirements in critical care. *N Engl J Med* 1999; **340:** 409–17.
9 Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA* 2010; **304:** 1559–67.
10 Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011; **365:** 2453–62.
11 Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin thresholds for transfusion in septic shock. *N Engl J Med* 2014; **371:** 1381–91.
12 Pape A, Stein P, Horn O, et al. Clinical evidence of blood transfusion effectiveness. *Blood Transfus* 2009; **7:** 250–58.

Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial

Vipul Jairath, Brennan C Kahan, Alasdair Gray, Caroline J Doré, Ana Mora, Martin W James, Adrian J Stanley, Simon M Everett, Adam A Bailey, Helen Dallal, John Greenaway, Ivan Le Jeune, Melanie Darwent, Nicholas Church, Ian Reckless, Renate Hodge, Claire Dyer, Sarah Meredith, Charlotte Llewelyn, Kelvin R Palmer, Richard F Logan, Simon P Travis, Timothy S Walsh, Michael F Murphy

Summary

Background Transfusion thresholds for acute upper gastrointestinal bleeding are controversial. So far, only three small, underpowered studies and one single-centre trial have been done. Findings from the single-centre trial showed reduced mortality with restrictive red blood cell (RBC) transfusion. We aimed to assess whether a multicentre, cluster randomised trial is a feasible method to substantiate or refute this finding.

Methods In this pragmatic, open-label, cluster randomised feasibility trial, done in six university hospitals in the UK, we enrolled all patients aged 18 years or older with new presentations of acute upper gastrointestinal bleeding, irrespective of comorbidity, except for exsanguinating haemorrhage. We randomly assigned hospitals (1:1) with a computer-generated randomisation sequence (random permuted block size of 6, without stratification or matching) to either a restrictive (transfusion when haemoglobin concentration fell below 80 g/L) or liberal (transfusion when haemoglobin concentration fell below 100 g/L) RBC transfusion policy. Neither patients nor investigators were masked to treatment allocation. Feasibility outcomes were recruitment rate, protocol adherence, haemoglobin concentration, RBC exposure, selection bias, and information to guide design and economic evaluation of the phase 3 trial. Main exploratory clinical outcomes were further bleeding and mortality at day 28. We did analyses on all enrolled patients for whom an outcome was available. This trial is registered, ISRCTN85757829 and NCT02105532.

Findings Between Sept 3, 2012, and March 1, 2013, we enrolled 936 patients across six hospitals (403 patients in three hospitals with a restrictive policy and 533 patients in three hospitals with a liberal policy). Recruitment rate was significantly higher for the liberal than for the restrictive policy (62% *vs* 55%; p=0·04). Despite some baseline imbalances, Rockall and Blatchford risk scores were identical between policies. Protocol adherence was 96% (SD 10) in the restrictive policy *vs* 83% (25) in the liberal policy (difference 14%; 95% CI 7–21; p=0·005). Mean last recorded haemoglobin concentration was 116 (SD 24) g/L for patients on the restrictive policy and 118 (20) g/L for those on the liberal policy (difference –2·0 [95% CI –12·0 to 7·0]; p=0·50). Fewer patients received RBCs on the restrictive policy than on the liberal policy (restrictive policy 133 [33%] *vs* liberal policy 247 [46%]; difference –12% [95% CI –35 to 11]; p=0·23), with fewer RBC units transfused (mean 1·2 [SD 2·1] *vs* 1·9 [2·8]; difference –0·7 [–1·6 to 0·3]; p=0·12), although these differences were not significant. We noted no significant difference in clinical outcomes.

Interpretation A cluster randomised design led to rapid recruitment, high protocol adherence, separation in degree of anaemia between groups, and non-significant reduction in RBC transfusion in the restrictive policy. A large cluster randomised trial to assess the effectiveness of transfusion strategies for acute upper gastrointestinal bleeding is both feasible and essential before clinical practice guidelines change to recommend restrictive transfusion for all patients with acute upper gastrointestinal bleeding.

Funding NHS Blood and Transplant Research and Development.

Introduction

Acute upper gastrointestinal bleeding accounts for 70 000 admissions every year to UK hospitals[1] and for 11% of all red blood cells (RBCs) transfused in England.[2] Despite being the most common single indication for RBC transfusion, the optimum threshold for transfusion is uncertain.[3] Findings from randomised trials in other cohorts such as those who have had cardiac surgery,[4] are in critical care,[5] or have had hip surgery[6] have shown that thresholds for transfusion can be safely lowered without adversely affecting outcomes. Whether a restrictive approach to transfusion can safely be extrapolated to elderly patients with acute bleeding or cardiovascular disease is unclear,[7–10] which is particularly relevant to patients with acute upper gastrointestinal bleeding, in whom the burden of comorbidity is often high.[3,11]

Findings from cohort studies suggest associations between RBC transfusion after acute upper gastrointestinal bleeding and adverse clinical outcomes.[12,13] Investigators of a single-centre, randomised controlled trial[14] that took place for 6 years in a specialist

Published Online May 6, 2015 http://dx.doi.org/10.1016/S0140-6736(14)61999-1

See Online/Comment http://dx.doi.org/10.1016/S0140-6736(14)62351-5

NHS Blood and Transplant, Oxford, UK (V Jairath MRCP, Prof M F Murphy FRCPath); **Translational Gastroenterology Unit, Nuffield Department of Medicine, University of Oxford, Oxford, UK** (V Jairath, A A Bailey FRACP, S P Travis FRCP); **Medical Research Council Clinical Trials Unit at University College London, London, UK** (B C Kahan MSc, C J Doré BSc, S Meredith MFPHM); **Department of Emergency Medicine** (A Gray FCEM), **and Department of Gastroenterology** (N Church MRCP), **Royal Infirmary of Edinburgh, Edinburgh, UK; NHS Blood and Transplant Clinical Trials Unit, Cambridge, UK** (A Mora PhD, R Hodge MSc, C Dyer BSc, C Llewelyn PhD); **National Institute for Health Research Nottingham Digestive Diseases Biomedical Research Unit** (M W James MRCP, Prof R F Logan FRCP), **and Department of Research and Education in Emergency Medicine, Acute Medicine and Trauma** (I Le Jeune MRCP), **Nottingham University Hospitals NHS Trust, Nottingham, UK; Gastrointestinal Unit, Glasgow Royal Infirmary, Glasgow, UK** (A J Stanley FRCP); **Department of Gastroenterology, St James's University Hospital, Leeds, UK** (S M Everett MRCP); **Department of Gastroenterology, James Cook University Hospital, Middlesbrough, UK** (J Greenaway FRCP, H Dallal FRCP); **Department of**

Emergency Medicine (M Darwent FCEM), **and Department of Acute General Medicine** (I Reckless MRCP), **Oxford University Hospitals NHS Trust, Oxford, UK; Western General Hospital, Edinburgh, UK** (K R Palmer FRCP); **Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK** (Prof T S Walsh FRCP); **and National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospitals, Oxford, UK** (Prof M F Murphy FRCPath)

Correspondence to:
Dr Vipul Jairath, Translational Gastroenterology Unit, Nuffield Department of Medicine, University of Oxford, Oxford OX3 9DU, UK
vipul.jairath@nhsbt.nhs.uk

gastrointestinal bleeding unit in Barcelona, Spain, reported reduced mortality and rebleeding with implementation of restrictive transfusion for acute upper gastrointestinal bleeding. However, these results are unlikely to be generalisable to routine clinical practice because of exclusion of patients with major cardiovascular comorbidity, stringent processes of care, and differing case mix.[3] A large, pragmatic, multicentre trial is essential to either substantiate or refute these findings before clinical practice guidelines are changed worldwide to recommend restrictive transfusion for all patients with acute upper gastrointestinal bleeding. Because acute upper gastrointestinal bleeding is a medical emergency that can need early transfusion and many care providers, a trial that needs adherence to transfusion strategies across many centres would be challenging to do.

In the Transfusion in Gastrointestinal Bleeding Trial (TRIGGER), we aimed to assess whether a restrictive or liberal RBC transfusion policy for acute upper gastrointestinal bleeding in routine clinical practice is feasible and safe to implement through cluster randomisation, and did an exploratory analysis of the major clinical effects, enrolling all new adult admissions, irrespective of their comorbidity (except for exsanguinating haemorrhage) or age.

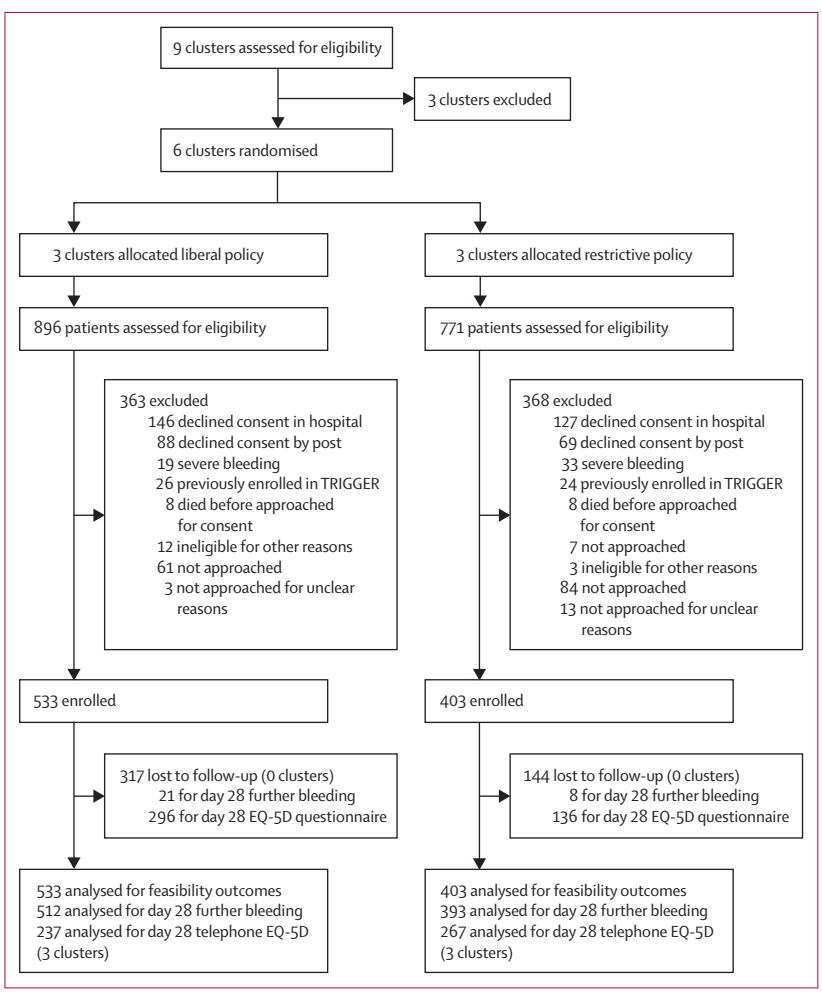


Figure 1: **Trial profile**

Methods

Study design and patients

We did this pragmatic, multicentre, open-label, cluster randomised feasibility trial of a restrictive versus liberal RBC transfusion policy in adults with acute upper gastrointestinal bleeding in the UK to inform the feasibility and design of a phase 3 trial. Because of the need for immediate implementation of an RBC transfusion policy from first presentation until discharge, across several specialty groups in different clinical areas of a hospital, we chose a cluster design to simplify intervention delivery and reduce contamination between policies. We deemed a feasibility trial essential to establish whether clinician behaviour could be changed on a hospital-wide scale and to assess potential for selection bias or outcome-reporting bias because of the open-label nature of the study. A rationale and methodology study has been published,[15] and the full protocol is available online.

Hospitals were eligible if they had more than 20 acute upper gastrointestinal bleeding admissions monthly, more than 400 adult beds, endoscopy available 24 h a day, onsite access to intensive care and surgery, and staff willing to be randomly allocated to and implement a transfusion policy for all new acute upper gastrointestinal bleeding admissions. Patients were eligible if they presented with new acute upper gastrointestinal bleeding (defined by haematemesis or melaena) and were aged 18 years or older; the only exclusion criterion was exsanguinating haemorrhage, for which we provided objective guidance criteria (appendix p 1). We sought written informed consent from individual patients or their representatives for use of routine hospital records and telephone follow-up at day 28. Ethics approval was granted in England (National Research Ethics Service Committee South Central—Oxford C; reference 12/SC/0062) and Scotland (Scotland A Research Ethics Committee; reference 12/SS/0023).

Randomisation and masking

We randomly allocated (using a computer-generated randomisation sequence) centres to a transfusion policy using a random permuted block of six (three hospitals per policy), without stratification or matching (randomisation done by BCK). We identified patients from emergency departments and acute admissions units. All clinicians, patients, and outcome assessors were unmasked to treatment allocation.

Procedures

For the restrictive policy, patients were eligible for RBC transfusion when their haemoglobin concentration fell below 80 g/L, with a post-transfusion target of 81–100 g/L.

For the liberal policy, patients were eligible when their haemoglobin concentration fell below 100 g/L, with a post-transfusion target of 101–120 g/L. These thresholds were informed by present UK transfusion practice.[15] The number of RBC units transfused and the timing of repeat haemoglobin concentration measurements was per clinician discretion. All clinicians could deviate from the policy, but were asked to document the reason. In keeping with the pragmatic design no other aspects of care were protocol driven, although clinicians were encouraged to follow evidence-based guidelines.[16,17]

A lead clinician championed the study at each site, supported by a coinvestigator from an allied acute specialty. We used a multifaceted approach to implement the policy, including the daily presence of a research nurse in acute areas, regular attendance by a member of the trial team at medical and nursing handovers in acute areas to reinforce the policy, departmental and grand round presentations, posters, regular email reminders, and a flagging system in transfusion laboratories to remind doctors and transfusion laboratory scientific staff of the policy whenever a transfusion request for acute upper gastrointestinal bleeding occurred.

Outcomes

We collected both feasibility outcome measures and exploratory clinical outcome measures, listed in the study protocol. Feasibility outcomes were recruitment rate, adherence to transfusion policy (overall, per patient, and per haemoglobin count), difference in haemoglobin concentration between groups, RBC exposure, evidence of selection bias, and information to guide the design and economic evaluation of the phase 3 trial. We measured haemoglobin concentrations (during the first 7 days, the entire follow-up, and before discharge), the proportion of patients receiving at least one RBC transfusion, and the number of units transfused. Clinical outcomes included further bleeding, thromboembolic and ischaemic events, and number of infections (inhospital and day 28, with day 28 being the main analysis timepoint). We also assessed mortality, serious adverse events, and health-related quality of life (with Euroqol EQ-5D questionnaire) at day 28, and need for therapeutic intervention at index endoscopy, need for surgery or radiological intervention to control bleeding, and transfusion reactions.

Statistical analysis

On the basis of our predicted sample size of 849 patients, we estimated the precision with which we would be able to detect a difference in the mean Rockall[18] score between treatment policies, which might show selection bias. With a two-sided significance level of 5%, an intracluster correlation coefficient of 0·033, and an SD of 1·84, 849 patients would provide 92% power to detect a mean difference of one point.[15]

	Liberal policy (n=533)	Restrictive policy (n=403)
Baseline characteristics		
Male	322 (60%)	244 (61%)
Age (years)	60·4 (20·0)	58·0 (20·3)
Rockall score*	2 (1–4)	2 (1–4)
Blatchford score†	6 (2–10)	6 (1–9)
Signs and symptoms		
Melaena‡	266 (50%)	209 (52%)
Haematemesis	302 (57%)	209 (52%)
Heart rate (beats per min)§	95·6 (20·1)	94·8 (21·8)
Systolic blood pressure (mm Hg)¶	125·9 (22·7)	126·9 (22·8)
Pre-existing comorbidities		
Ischaemic heart disease	76 (14%)	61 (15%)
Cardiac failure‖	21 (4%)	18 (4%)
Hypertension‖	109 (20%)	123 (31%)
Respiratory disease‖	74 (14%)	84 (21%)
Renal disease	36 (7%)	18 (4%)
Liver disease	91 (17%)	45 (11%)
Malignancy‖	58 (11%)	41 (10%)
Stroke‖	34 (6%)	25 (6%)
First recorded laboratory data		
Haemoglobin (g/L)	114 (34)	119 (32)
Urea (mmol/L)**	10·2 (7·2)	10·0 (7·6)
Albumin (g/L)††	36 (8)	38 (7)
Lowest haemoglobin during follow-up		
≤79 g/L	146 (27%)	118 (29%)
80–99 g/L	146 (27%)	69 (17%)
100–120 g/L	91 (17%)	70 (17%)
≥121 g/L	149 (28%)	146 (36%)
Medications and fluids		
Proton pump inhibitor (pre-endoscopy)	270 (53%)	225 (56%)
Iron (oral or intravenous)‡‡	47 (9%)	43 (11%)
Any intravenous fluids§§	412 (81%)	297 (75%)
Colloid volume in 24 h	0·2 (0·6)	0·1 (0·4)
Crystalloid volume in 24 h	1·6 (1·4)	1·9 (1·7)
Platelets¶¶	13 (2%)	13 (3%)
Fresh frozen plasma¶¶	22 (4%)	24 (6%)
Cryoprecipitate¶¶	1 (<1%)	2 (<1%)
Source of bleeding‖‖		
Peptic ulcer	94 (24%)	59 (20%)
Gastro-oesophageal varix	56 (15%)	25 (8%)
Oesophagitis/gastritis/duodenitis	89 (23%)	82 (28%)
Mallory-Weiss tear	8 (2%)	22 (8%)
Malignancy	13 (3%)	9 (3%)
Non-identified	60 (16%)	49 (17%)
Other	67 (17%)	40 (16%)

Data are n (%), mean (SD), or median (IQR). *Data missing for one patient in the liberal policy. †Data missing for one patient in the liberal policy and six in the restrictive policy. ‡Data missing for two patients in the liberal policy. §Data missing for two patients in the liberal policy and one in the restrictive policy. ¶Data missing for one patient in the restrictive policy. ‖Data missing for one patient in the liberal policy. **Data missing for two patients in the liberal policy and nine in the restrictive policy. ††Data missing for 53 patients in the liberal policy and 37 in the restrictive policy. ‡‡Data missing for 24 patients in the liberal policy and 11 in the restrictive policy. §§Data missing for 24 patients in the liberal policy and eight in the restrictive policy. ¶¶Data missing for nine patients in the liberal policy and one in the restrictive policy. ‖‖Endoscopy not performed for 146 patients in the liberal policy and 117 in the restrictive policy.

Table 1: **Baseline characteristics, laboratory variables, and cointerventions**

For the **study protocol** see http://www.nhsbt.nhs.uk/trigger/documents/study-protocol/TRIGGER_%20Protocol.pdf

See Online for appendix

	Liberal policy			Restrictive policy			p value for difference between treatment policies
	Enrolled (n=533)	Not enrolled (n=363)	Difference	Enrolled (n=403)	Not enrolled (n=368)	Difference	
Age (years)	59·9 (20·0)	53·9 (23·4)	5·2	57·4 (20·3)	59·8 (23·6)	−2·6	0·05
Haemoglobin concentration (g/L)	115 (34)	128 (31)	−10	119 (32)	126 (27)	−4·0	0·08
Rockall score	2·3 (1·8)	1·7 (1·9)	0·6	2·4 (2·1)	2·5 (1·9)	−0·1	0·07
Blatchford score	6·1 (4·6)	3·8 (4·1)	2·4	5·8 (4·6)	4·7 (4·5)	1·3	0·07

Data are mean (SD).

Table 2: **Differences between eligible patients who were enrolled versus those not enrolled**

	Liberal policy	Restrictive policy	Treatment effect*	p value
All enrolled patients†				
Overall adherence‡	83% (25)	96% (10)	14% (7 to 21)	0·005
Patients receiving at least one transfusion	247 (46%)	133 (33%)	−12% (−35 to 11)	0·23
Number of units transfused	1·9 (2·8)	1·2 (2·1)	−0·7 (−1·6 to 0·3)	0·12
Mean haemoglobin over entire follow-up (g/L)	115 (23)	115 (26)	−1·0 (−12·0 to 11·0)	0·90
Last recorded haemoglobin (g/L)	118 (20)	116 (24)	−2·0 (−12·0 to 7·0)	0·50
Patients with haemoglobin concentration <120 g/L§				
Overall adherence	76% (27)	94% (12)	19% (11 to 26)	0·003
Patients receiving at least one transfusion	246 (64%)	132 (51%)	−12% (−36 to 12)	0·24
Number of units transfused	2·6 (3·0)	1·8 (2·5)	−0·8 (−1·9 to 0·3)	0·12
Mean haemoglobin over entire follow-up (g/L)	103 (13)	98 (15)	−5 (−13 to 3)	0·18
Last recorded haemoglobin before discharge (g/L)	107 (12)	101 (13)	−7 (−14 to 0)	0·05
Patients with haemoglobin concentration <100 g/L¶				
Overall adherence	69% (28)	93% (14)	24% (16 to 32)	0·001
Patients receiving at least one transfusion	242 (83%)	130 (68%)	−14% (−32 to 4)	0·09
Number of units transfused	3·4 (3·0)	2·4 (2·6)	−1·0 (−2·0 to 0·01)	0·05
Mean haemoglobin over entire follow-up (g/L)‖	98 (10)	92 (10)	−6 (−11 to −1)	0·02
Last recorded haemoglobin before discharge (g/L)**	105 (12)	96 (11)	−9 (−14 to −4)	0·007

Data are mean (SD) or n (%). *Treatment effects are differences in means for continuous outcomes, and differences in percentages for binary outcomes. †Liberal policy: n=533; restrictive policy: n=403. ‡Overall adherence refers to the proportion of haemoglobin counts for which no deviation from the transfusion policy occurred for each patient. §Liberal policy: n=383; restrictive policy: n=257. ¶Liberal policy: n=293; restrictive policy: n=190. ‖18 patients had missing data and were excluded from this analysis (16 liberal and two restrictive). **50 patients had missing data and were excluded from this analysis (37 liberal and 13 restrictive).

Table 3: **Protocol adherence, red blood cell transfusion, and haemoglobin results**

The statistical analysis plan was published before database lock.[19] All analyses were predefined unless otherwise stated. We did analyses on all enrolled patients for whom an outcome was available. We also did analyses on all enrolled patients with a haemoglobin concentration of less than 120 g/L during follow-up because this group was expected to be most likely to receive a transfusion and be affected by the treatment policy.

We analysed feasibility and clinical outcomes using cluster-level summaries, giving equal weight to each cluster.[20,21] We presented results as a difference in means for continuous outcomes, and a difference in proportions for binary outcomes. Prespecified subgroup analyses and post-hoc analyses are listed in the appendix p 3.

We did all analyses with Stata/IC 12.1. This trial is registered, ISRCTN85757829 and NCT02105532.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data analysis, data interpretation, or writing of the report. The writing committee had full access to all the data in the study and had final responsibility for the decision to submit to publication. BCK and CJD are statistical guarantors.

Results

Between Sept 3, 2012, and March 1, 2013, 1667 patients were admitted to the six university hospitals in the UK participating in the trial with acute upper gastrointestinal bleeding, of whom 1600 (96%) were eligible and 936 (59%) of whom we enrolled: 533 (57%) into the liberal RBC transfusion policy and 403 (43%) into the restrictive policy (figure 1). Recruitment rate was significantly higher in the liberal policy than the restrictive policy (62% *vs* 55%; p=0·04). 3% were ineligible because of exsanguinating bleeding (liberal group 19 [2%] of 896; restrictive group 33 [4%] of 771; p=0·08). The commonest reason for non-enrolment was consent refusal for data collection and telephone follow-up, which occurred in 430 (27%) of the 1600 eligible patients. Data for further bleeding at day 28 were missing in 29 (3%) of 936 patients randomly allocated, who we excluded from analysis. Telephone contact at day 28 to administer an EQ-5D questionnaire was not possible in 136 (34%) of 403 participants in the restrictive policy and 296 (56%) of 533 in the liberal policy.

Baseline characteristics were similar in terms of Rockall and Blatchford risk scores, blood pressure, heart rate, and symptoms of bleeding (table 1, appendix p 2). Some baseline imbalances in comorbidities existed, with a greater proportion of patients in the liberal policy than the restrictive policy with liver disease, whereas more patients in the restrictive policy had respiratory disease or hypertension. Ischaemic heart disease was

similar between treatment groups. In the liberal policy, patients enrolled were older than those not enrolled compared with the restrictive policy, in which patients enrolled were younger than those not enrolled (table 2).

Overall adherence to the transfusion protocol (mean number of haemoglobin counts with no deviations, per patient) was significantly higher in the restrictive policy (96%; SD 10) than the liberal policy (83%; SD 25; difference 14% [95% CI 7–21]; p=0·005), with a similar pattern noted in patients with a haemoglobin concentration of less than 120 g/L (restrictive policy 94% [SD 12] *vs* liberal policy 76% [27]; difference 19% [95% CI 11–26]; p=0·003) (table 3). Adherence each month was consistent in the restrictive policy, but decreased over time in the liberal policy (figure 2). In the liberal policy, 675 (24%) of 2769 of all haemoglobin measurements led to a protocol deviation (672 no transfusion when haemoglobin concentration was less than 100 g/L; three transfusions when haemoglobin concentration was 100 g/L or higher), compared with 93 (5%) of 1754 in the restrictive group (67 no transfusion when haemoglobin concentration was less than 80 g/L; 26 transfusions when haemoglobin concentration was 80 g/L or higher).

247 (46%) of 533 patients allocated to the liberal policy were transfused compared with 133 (33%) of 403 patients allocated to the restrictive policy (difference –12%; 95% CI –35 to 11; p=0·23; table 3). The mean number of units transfused was lower in the restrictive policy than the liberal policy, although this difference was not significant (restrictive policy 1·2 [SD 2·1]; liberal policy 1·9 [2·8]; difference –0·7 [95% CI –1·6 to 0·3]; p=0·12). In patients with a haemoglobin concentration of less than 120 g/L, concentration at hospital discharge was significantly lower in the restrictive policy than in the liberal policy (restrictive policy 101 g/L [SD 13]; liberal policy 107 g/L [12]; difference –7 g/L, 95% CI –14 to 0; p=0·05) (figure 3). In patients with a haemoglobin concentration of less than 100 g/L, mean concentration during the entire follow-up and at discharge was significantly lower in the restrictive policy than the liberal policy (table 3). We noted no significant differences in clinical outcomes or mean EQ-5D scores between treatment groups (table 4).

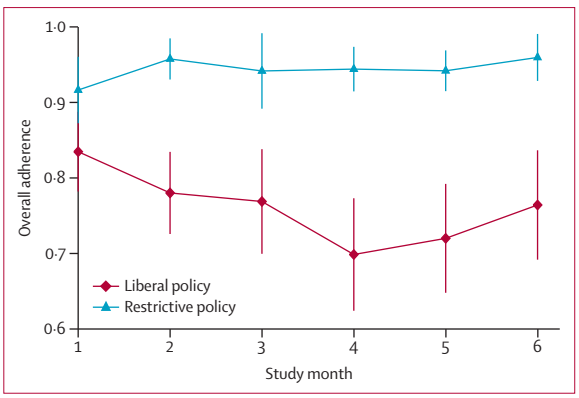


Figure 2: **Overall adherence to transfusion policy by study month (patients with a haemoglobin concentration of less than 120 g/L)**

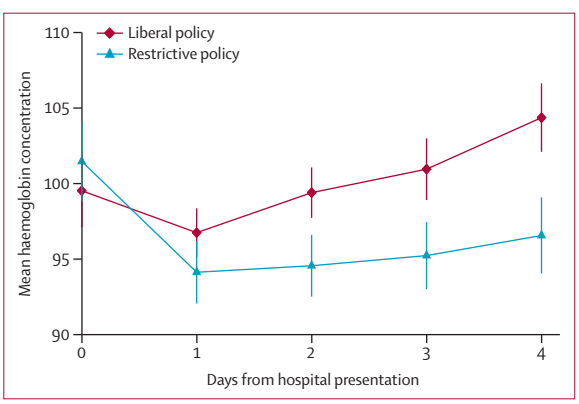


Figure 3: **Mean haemoglobin concentration over time (patients with haemoglobin concentration of less than 120 g/L)**

Discussion

We report the first multicentre randomised trial comparing transfusion strategies for acute upper gastrointestinal bleeding, gathering evidence for the feasibility of a phase 3 trial (panel). The pragmatic eligibility criteria meant that 96% of patients admitted to the six hospitals during the recruitment period were eligible, of whom almost 60% were enrolled. The cluster design was acceptable to clinicians, resulted in an efficient recruitment rate, and enabled implementation of the transfusion policy hospital-wide, alongside routine clinical care. High adherence to both transfusion policies was achieved, resulting in a 13% absolute reduction in the proportion of patients transfused in the restrictive policy, reduction in the amount of blood transfused between treatment policies, and separation in haemoglobin concentration, although none of these between-group differences were significant. The small, non-significant reduction in mean number of RBC units transfused was in keeping with that reported in a meta-analysis of transfusion trigger trials.[26]

Protocol adherence was better in the restrictive policy than the liberal policy—restrictive policy protocol adherence was consistent throughout the trial. In the liberal policy, most violations were due to RBCs not being administered below the threshold of 100 g/L. This greater adherence to the restrictive policy than the liberal policy could be due to clinician bias towards low transfusion thresholds for acute upper gastrointestinal bleeding, particularly for low-risk patients, extrapolated from evidence of the safety of restrictive transfusion in trials of critical care,[5] cardiac surgery,[4] and hip surgery.[10] Our liberal threshold of 100 g/L was informed by actual UK transfusion practice at the time the study was designed in 2009. Guidelines advocating restrictive transfusion for acute upper gastrointestinal bleeding are based on one trial done in an intensive care population[5] in which patients with acute bleeding were specifically excluded; transfusion requirements might

	Liberal policy (n=383)	Restrictive policy (n=257)	Treatment effect*
Further bleeding†			
Day 28	31 (9%)	13 (5%)	−4 (−12 to 5)
Hospital discharge	24 (6%)	9 (4%)	−3 (−13 to 7)
All-cause mortality‡			
Day 28	25 (7%)	14 (5%)	−1 (−8 to 6)
Thromboembolic or ischaemic events§			
Day 28	23 (7%)	9 (4%)	−4 (−10 to 3)
Hospital discharge	21 (5%)	7 (3%)	−3 (−9 to 2)
Surgical or radiological intervention			
Hospital discharge	11 (3%)	10 (4%)	1 (−4 to 6)
Acute transfusion reactions¶			
Hospital discharge	9 (2%)	2 (1%)	−2 (−4 to 1)
Therapeutic intervention			
Hospital discharge	144 (38%)	81 (32%)	−7 (−25 to 11)
Infections‖			
Hospital discharge	92 (24%)	67 (26%)	1 (−25 to 27)
Length of hospital stay (days)**			
Hospital discharge	5 (3–9)	4 (3–7)	−1 (−2 to 0)
EQ-5D††			
Day 28	0·69 (0·32)	0·76 (0·27)	0·07 (−0·10 to 0·23)
Serious adverse events‡‡			
Day 28	83 (22%)	45 (18%)	−5 (−23 to 13)

Data are n (%), median (IQR), mean (SD), or effect (95% CI). *Treatment effects are differences in means for continuous outcomes and differences in percentages for binary outcomes. †27 patients had missing data and were excluded from this analysis (19 liberal and eight restrictive). ‡One patient had missing data in the liberal group and was excluded from this analysis. §48 patients had missing data and were excluded from this analysis (33 liberal and 15 restrictive). ¶Five patients had missing data and were excluded from this analysis (three liberal and two restrictive). ‖One patient had missing data in the liberal group and was excluded from this analysis. **31 patients had missing data and were excluded from this analysis (21 liberal and ten restrictive). ††295 patients had missing data and were excluded from this analysis (214 liberal and 81 restrictive). ‡‡One patient in the liberal group was missing data and was excluded from this analysis.

Table 4: **Clinical outcomes (patients with haemoglobin concentration of less than 120 g/L)**

reasonably be expected to differ after acute bleeding because of rapid development of anaemia and haemodynamic compromise. For the phase 3 trial, we plan to lower the threshold for transfusion in the liberal group to take account of this changing practice and we would also exclude low-risk patients (with a Rockall score of 0) who are unlikely to be transfused.

The greater protocol adherence in the restrictive than the liberal policy might also have been influenced by the Barcelona trial of transfusion strategies for gastrointestinal bleeding,[14] published during recruitment to TRIGGER. In this single-centre trial, improved survival and rebleeding rates were noted in patients transfused below a haemoglobin concentration of 70 g/L compared with those transfused below 90 g/L. Whether these results could be collected in other hospitals, particularly in the UK, is questionable on several grounds. First, a high proportion of the trial population had liver cirrhosis and variceal bleeding, and a treatment effect was only seen in patients for whom mechanisms of bleeding differ and who account for only 10% of UK presentations with acute upper gastrointestinal bleeding. Second, the trial excluded patients with major comorbidities, including ischaemic heart disease, vascular disease, or stroke, which excludes almost 40% of all UK presentations with acute upper gastrointestinal bleeding,[27] representing the group at greatest potential of complications from acute anaemia. Third, processes of care are unlikely to be reproducible at other institutions, specifically delivery of therapeutic endoscopy to all patients within 6 h, which might affect transfusion use. Furthermore, single-centre trials tend to find larger treatment effects than multicentre trials,[28] highlighting the risk of strong recommendations on the basis of a single-centre trial.[28,29]

Despite some baseline imbalances, participants in each policy had similar risk scores and haemodynamic status. Patients enrolled in the liberal policy were older than those not enrolled, whereas in the restrictive group, patients enrolled were younger than those not enrolled. These differences are probably chance imbalances due to the small number of clusters. For the main trial, about 30 clusters would need to be randomly allocated, which should achieve acceptable balance between treatment arms. Prespecified covariate adjustment would account for any unexpected baseline imbalances in important prognostic factors.[30] Baseline imbalances could have been due to selection bias because of the open-label nature of the study. Prevention of selection bias will be important in the phase 3 trial. A potential solution would be to seek a consent waiver for anonymous data collection to allow routinely collected data to be summarised for all eligible participants.

TRIGGER was not a phase 3 trial, so its clinical outcomes should not be used to inform clinical practice directly. A key area of uncertainty in transfusion practice concerns safe transfusion thresholds in patients with ischaemic heart disease,[8,10,31] particularly relevant to acute upper gastrointestinal bleeding; 14% of patients with acute upper gastrointestinal bleeds have ischaemic heart disease.[11,12] Findings from a pilot trial of transfusion strategies in patients with ischaemic heart disease[10] showed a 15% absolute increase in mortality in patients receiving transfusion at a threshold of haemoglobin concentration of 80 g/L compared with 100 g/L, a similar magnitude of excess mortality as that observed in TRIGGER (appendix, p 4), showing the need for further evidence before universal restrictive transfusion for acute upper gastrointestinal bleeding can be advocated.

This feasibility trial provides key learning points for design of the phase 3 trial. We plan to enrol the same patient population as in TRIGGER, using broad and inclusive eligibility criteria to promote efficient recruitment and generalisability, although we would exclude the lowest-risk patients who are unlikely to be recipients of transfusion. For high-risk patients with ischaemic heart or cerebrovascular disease who might be particularly susceptible to adverse effects of anaemia, we would ask the Independent Data Monitoring Committee to monitor serious adverse events and provide

recommendations at a formal interim analysis for their continued enrolment, and do a prespecified subgroup analysis for ischaemic heart disease. Despite the results of the Barcelona trial,[14] we would also enrol patients with liver cirrhosis because of the limitations of external validity in that trial. For the interventions, we plan to lower thresholds for transfusion to a haemoglobin concentration of 90 g/L in the liberal arm and to 70 g/L in the restrictive arm, which accounts for the uncertainty in present practice. Although previous transfusion strategy trials have used haemoglobin concentration as an entry criterion,[5,6,8,14] we designed this trial to assess the effect of implementation of a treatment policy on a hospital-wide scale for all patients presenting with acute upper gastrointestinal bleeding, and would repeat this efficient design for a phase 3 trial, but additionally incorporate a prespecified secondary analysis of clinical outcomes using the transfusion threshold in the liberal group as a cutoff.

The primary outcome for the phase 3 trial would be mortality. Our estimate of the intracluster correlation coefficient, essential for sample size calculation, was similar to that estimated from a UK audit of acute upper gastrointestinal bleeding,[27] which probably shows that both studies were pragmatic, recording all presentations with acute upper gastrointestinal bleeding. We would still randomly allocate by cluster to assess the treatment effect of a policy in a diverse patient population in routine clinical care, while minimising contamination. These benefits far outweigh the often-cited limitation of statistical inefficiency in cluster randomised trials, particularly since sufficient recruitment would not be a barrier in this trial; we estimate that although 15% more participants would need to be recruited through cluster randomisation than through individual randomisation, recruitment time would be almost 40% less, resulting in a more efficient trial design (appendix p 5). We believe that this design offers an attractive method of comparative effectiveness research in the NHS for treatment policies that are within the boundaries of normal care and that have clinical equipoise.

Patient consent for routine clinical data collection and telephone follow-up was lower than we expected. For the phase 3 trial, we would seek a consent waiver to enable analysis of routinely recorded inhospital data for all patients. The trial design would be more efficient through linkage to routine administrative data to record mortality and readmissions, which would allow follow-up for longer periods than would be possible without this data. Telephone follow-up at day 28 for patient-reported outcomes would be replaced by assessment of functional status at discharge to reduce attrition rates due to difficulties with telephone contact.

Reduction of RBC transfusion for acute upper gastrointestinal bleeding would have substantial financial implications for health-care agencies. In 2013–14, 1·7 million units of RBCs were issued in England, with an estimated 204 000 units for acute upper gastrointestinal bleeding alone, costing UK£123·31 per unit.[32] A 13% reduction, as shown in this trial, would lead to annual savings to the NHS of about £3·3 million for the blood alone, which excludes blood transfusion laboratory and blood administration costs.

We used a pragmatic cluster randomised design to show the feasibility of implementation of hospital-wide transfusion policies for acute upper gastrointestinal bleeding, resulting in a non-significant reduction in blood use and separation in haemoglobin concentration. A large, cluster randomised phase 3 trial to assess the effectiveness of transfusion strategies for acute upper gastrointestinal bleeding is now essential before practice guidelines are changed to recommend restrictive transfusion for all patients with acute upper gastrointestinal bleeding.

Panel: Research in context

Systematic review

We did a Cochrane review of randomised controlled trials comparing red blood cell (RBC) transfusion strategies for acute upper gastrointestinal bleeding in 2008, and updated it in 2010.[22] We identified three underpowered trials of 93 participants.[23–25] The small numbers of participants, missing data, and methodological deficiencies did not allow meaningful conclusions, justifying the need for a trial of transfusion strategies for acute upper gastrointestinal bleeding. We have identified one single-centre trial from Barcelona,[14] which started in 2003 and had the report published in 2013, halfway through TRIGGER recruitment. Investigators of this trial reported a reduction in mortality and rebleeding with restrictive transfusion and thus recommended restrictive transfusion for acute upper gastrointestinal bleeding. The population in this trial differed from ours because a third of participants had liver cirrhosis for which the mechanism of bleeding differs and the investigators excluded patients with cardiovascular comorbidity and used care processes unlikely to be generalisable to most health-care institutions.[3]

Interpretation

In our trial, the randomised transfusion policies were successfully implemented on a hospital-wide scale across different specialty groups and clinical areas for 6 months, with a high level of protocol adherence, leading to a non-significant reduction in RBC exposure in the restrictive policy and separation in haemoglobin concentration between treatment groups. We did not note any significant differences in clinical outcomes, although the trial was not powered for these outcomes. If restrictive transfusion is proven to be safe and effective in a large, similarly pragmatic trial, this trial would have the potential to safely reduce use of RBCs for the largest single indication for transfusion in England, and might have broad implications for restrictive use of RBCs after acute haemorrhage. A large cluster randomised trial is feasible and essential to do before clinical practice guidelines recommend restrictive transfusion for all patients with acute upper gastrointestinal bleeding.

Contributors

VJ and MFM conceived of the study. VJ, BCK, AG, CJD, SM, CL, KRP, RFL, SPT, TSW, and MFM designed the study. AM, MWJ, AJS, SME, AAB, HD, JG, ILJ, MD, NC, IR, RH, and CD acquired data. BCK analysed data. VJ, BCK, AG, CJD, MWJ, AJS, RFL, SPT, TSW, and MFM interpreted data. VJ and BCK drafted the report. AG, CJD, AM, MWJ, AJS, SME, AAB, HD, JG, ILJ, MD, NC, IR, RH, CD, SM, CL, KRP, RFL, SPT, TSW, and MFM revised the report for important intellectual content. All authors approved the final version.

TRIGGER trial collaboration

Trial Management Group: V Jairath, M Murphy, B Kahan, M James, A Gray, T Walsh, E Stokes, A Stanley, C Dyer, A Mora, R Hodge, C Llewelyn. *Independent Data Monitoring Committee:* M Greaves (chair), R Walt, M Turner, K Wheatley. *Trial Steering Committee:* C Hawkey (chair), D Wyncoll, J Benger, T Walsh, R Logan, C Doré, H Campbell, C Gorton (independent, lay member), S Meredith, C Llewelyn.

Participating hospitals and personnel (number of patients enrolled)

Royal Infirmary of Edinburgh, Edinburgh, UK (201): A Gray, N Church, L Mason, J Dear, K Keffala, R O'Brien, A Glover. *Queen's Medical Centre, Nottingham, UK (191)*: M James, I Le Jeune, L Mannion, R Foster. *Glasgow Royal Infirmary, Glasgow, UK (188)*: A Stanley, A Cahill, E Forrest, J Morris, J Winter, N Jamieson, D Gaya, S Barclay, N Dignon, S Taylor, A Cameron, R Gillespie, R Boyle, S Thornton, J Johnston. *St James's University Hospital, Leeds, UK (154)*: S Everett, P Mundre, S Muntaz, R Fazakerley, S Fox. *John Radcliffe Hospital, Oxford, UK (111)*: A Bailey, S Davies, S Beer, I Reckless, M Darwent, R Palmer, J East, J Collier, S Keshav, E Barnes. *James Cook University Hospital, Middlesbrough, UK (91)*: H Dallal, J Greenaway, D Joy, J McGivern, M Branch.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was funded by NHS Blood and Transplant Research and Development (grant number 10-09-CSU) and run by the NHS Blood and Transplant Clinical Trials Unit (formerly NHS Blood and Transplant/ Medical Research Council Clinical Trials Unit). The views and opinions expressed herein are those of the authors and do not necessarily represent those of NHS Blood and Transplant. The trial was supported by the National Institute for Health Research Clinical Research Networks. We thank the independent members of the Trial Steering Committee and independent data monitoring committee, members of the lay focus group and patient panel who contributed to trial design, and Age UK Abingdon for allowing us to run a focus group with members of the public. We thank all clinical teams in participating centres for their support and following the transfusion policies.

References

1 Crooks C, Card T, West J. Reductions in 28-day mortality following hospital admission for upper gastrointestinal hemorrhage. *Gastroenterology* 2011; **141:** 62–70.
2 Tinegate H, Chattree S, Iqbal A, Plews D, Whitehead J, Wallis JP. Ten-year pattern of red blood cell use in the North of England. *Transfusion* 2013; **53:** 483–89.
3 Jairath V. Acute upper gastrointestinal bleeding—time for some new triggers? *Transfus Med* 2013; **23:** 139–41.
4 Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA* 2010; **304:** 1559–67.
5 Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; **340:** 409–17.
6 Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011; **365:** 2453–62.
7 Walsh TS, Wyncoll DL, Stanworth SJ. Managing anaemia in critically ill adults. *BMJ* 2010; **341:** c4408.
8 Walsh TS, Boyd JA, Watson D, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. *Crit Care Med* 2013; **41:** 2354–63.
9 Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Crit Care Med* 2009; **37:** 3124–57.
10 Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J* 2013; **165:** 964–71. e1.
11 Crooks CJ, West J, Card TR. Comorbidities affect risk of nonvariceal upper gastrointestinal bleeding. *Gastroenterology* 2013; **144:** 1384–93, 1393. e1–2; quiz e18–19.
12 Hearnshaw SA, Logan RF, Palmer KR, Card TR, Travis SP, Murphy MF. Outcomes following early red blood cell transfusion in acute upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2010; **32:** 215–24.
13 Restellini S, Kherad O, Jairath V, Martel M, Barkun AN. Red blood cell transfusion is associated with increased rebleeding in patients with nonvariceal upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2013; **37:** 316–22.
14 Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; **368:** 11–21.
15 Jairath V, Kahan BC, Gray A, et al. Restrictive vs liberal blood transfusion for acute upper gastrointestinal bleeding: rationale and protocol for a cluster randomized feasibility trial. *Transfus Med Rev* 2013; **27:** 146–53.
16 Barkun AN. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2010; **152:** 101–13.
17 de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010; **53:** 762–68.
18 Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996; **38:** 316–21.
19 Kahan BC, Jairath V, Murphy MF, Dore CJ. Update on the transfusion in gastrointestinal bleeding (TRIGGER) trial: statistical analysis plan for a cluster-randomised feasibility trial. *Trials* 2013; **14:** 206.
20 Donner A, Klar N. Design and analysis of cluster randomization trials in health research. New York: Oxford University Press, 2000.
21 Hayes RJ, Moulton LH. Cluster randomised trials. Boca Raton: Chapman & Hall/Chemical Rubber Company, 2009.
22 Jairath V, Hearnshaw S, Brunskill SJ, et al. Red cell transfusion for the management of upper gastrointestinal haemorrhage. *Cochrane Database Syst Rev* 2010; **9:** CD006613.
23 Blair S, Janvrin S, McCollum C, et al. Effects of early blood transfusion on gastrointestinal haemorrhage. *Br J Surg* 1986; **73:** 783–85.
24 Elizalde J, Moitinho E, Garcia-Pagan J, et al. Effects of increasing blood hemoglobin levels on systemic hemodynamics of acutely anemic cirrhotic patients. *J Hepatol* 1998; **29:** 789–95.
25 Villarejo D, Rizzolo M, Lopez E, et al. Acute anemia in high digestive hemorrhage. Margins of security for their handling without transfusion of red globules. *Acta Gastroenterol Latinoam* 1999; **29:** 261–70.
26 Carless PA, Henry DA, Carson JL, Hebert PP, McClelland B, Ker K. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2010; **10:** CD002042.
27 British Society of Gastroenterology. UK comparative audit of upper gastrointestinal bleeding and the use of blood. Dec, 2007. www.bsg.org.uk/pdf_word_docs/blood_audit_report_07.pdf (accessed May 1, 2014).
28 Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. *Ann Intern Med* 2011; **155:** 39–51.
29 Bellomo R, Warrillow SJ, Reade MC. Why we should be wary of single-center trials. *Crit Care Med* 2009; **37:** 3114–19.
30 Kahan BC, Jairath V, Dore CJ, Morris TP. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials* 2014; **15:** 139.
31 Jairath V, Kahan BC, Logan RF, Travis SP, Palmer KR, Murphy MF. Red blood cell transfusion practice in patients presenting with acute upper gastrointestinal bleeding: a survey of 815 UK clinicians. *Transfusion* 2011; **51:** 1940–48.
32 NHS Blood and Transplant Annual Review 2012–2013. Blood supply. www.nhsbt.nhs.uk/annualreview/blood-supply (accessed May 1, 2014).