Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): pragmatic cluster randomised feasibility trial.

Authors

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Trial registration: The trial is registered as ISRCTN 85757829 and ClinicalTrials.gov NCT02105532

Key words: Transfusion, gastrointestinal bleeding, variceal bleeding, cluster randomization.

Word Count for abstract: 407
Word count for body of paper: 3218

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Abstract

Background: Transfusion thresholds for acute upper gastrointestinal bleeding (AUGIB) are controversial. To date there is only one relevant study, a single centre trial which reported reduced mortality with restrictive red blood cell (RBC) transfusion. Pragmatic studies are needed to confirm or refute this finding. We aimed to assess whether a multicentre cluster randomised trial was a feasible method of addressing this uncertainty.

Methods: TRIGGER was a pragmatic, open-label cluster randomised trial conducted in six university hospitals in the United Kingdom. Hospitals were randomly assigned (1:1) by a computer generated randomisation sequence (block size 6, without stratification) to either a restrictive (transfusion when haemoglobin (Hb) <80g/L) or liberal (transfusion when Hb <100g/L) RBC transfusion policy. All new adult presentations with AUGIB were eligible for enrolment, regardless of co-morbidity. Neither patients nor investigators were masked to treatment allocation. Main feasibility outcomes were recruitment rate, protocol adherence, Hb levels and RBC exposure. Main exploratory clinical outcomes were further bleeding and mortality at day 28. This study is registered with ClinicalTrials.gov (number NCT02105532) and ISRCTN (number 85757829).

Findings: Between September 2012 and March 2013, 1600 of 1667 (96%) participants were eligible and 936 of 1660 (59%) eligible participants were enrolled across six hospitals (three restrictive, 403 participants; three liberal, 533 participants). Despite some baseline imbalances, Rockall and Blatchford risk scores were identical between policies. Protocol adherence was 96% in the restrictive policy *vs.* 83% in the liberal policy) (difference 14%, 95% CI 7% to 21%). For the restrictive policy, Hb at discharge was lower (difference for patients with Hb<120 g/L -7·0; 95% CI -14·0 to 0.0) and fewer patients received RBCs (difference -13%, 95% CI -36 to 12%) with a mean of 0·8 (-1·9 to 0·3) fewer RBC units transfused. There was no significant difference in clinical outcomes: 28-day further bleeding, 5% (13 of 257) restrictive *vs.* 9% (31 of 383) liberal (difference -3·7%, 95% CI -12·2 to 4·8%); 28-day mortality, 5% (14 of 257) restrictive *vs.* 7% (25 of 383) liberal (difference -1·3%, 95% CI -8.0 to 5.5%).

Interpretation: Using a cluster randomised design led to rapid recruitment, high protocol adherence, separation in the degree of anaemia between groups and reduction in RBC transfusion in the restrictive policy. A larger cluster-randomised trial to assess the effectiveness of transfusion strategies for AUGIB is both feasible and essential to conduct before clinical practice guidelines change to recommend restrictive transfusion for all patients with AUGIB.

Funding: NHS Blood and Transplant R&D, grant 10-09-CSU.

Introduction

Acute Upper Gastrointestinal Bleeding (AUGIB) accounts for 70,000 admissions each year to UK hospitals (1) and 11% of all red blood cells (RBC) transfused in England (2). Despite being the most common single indication for RBC transfusion, the optimum threshold for transfusion is uncertain (3). Randomised trials in other critically ill cohorts have demonstrated that thresholds for transfusion can be safely lowered without adversely affecting outcomes (4-6). It is unclear whether a restrictive approach to transfusion can safely be extrapolated to older patients with acute bleeding or cardiovascular disease (7-10), which is particularly relevant to AUGIB where the burden of co-morbidity is high (3, 11).

Cohort studies suggest associations between RBC transfusion after AUGIB and adverse clinical outcomes (12-13). A recent single-centre randomised controlled trial (RCT) conducted over six years in a specialist gastrointestinal bleeding unit in Barcelona reported reduced mortality and rebleeding through implementation of restrictive transfusion for AUGIB (14). However, it is unlikely that these results are generalisable to routine clinical practice given the 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 confirm or refute these findings before clinical practice guidelines are changed worldwide. Since AUGIB is a medical emergency, can require early transfusion and involves numerous care-providers, conducting a trial which requires adherence to transfusion strategies across multiple centres would be challenging.

We conducted the Transfusion in Gastrointestinal Bleeding Trial (TRIGGER) to evaluate whether it was feasible and safe to implement a restrictive versus liberal RBC transfusion policy for AUGIB in routine clinical practice through cluster randomisation, as well as an exploratory analysis of the major clinical consequences, enrolling all new adult admissions regardless of their co-morbidity or age.

Methods

Study design and participants

TRIGGER was a pragmatic, cluster randomised trial of a restrictive versus liberal RBC transfusion policy in adults with AUGIB in the UK, conducted to inform the feasibility and design of a phase 3 trial. Due to the need for immediate implementation of a 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. A feasibility trial was considered essential to determine whether clinician behaviour could be changed on a hospital wide scale and to assess potential for selection bias or outcome reporting bias, given the open label nature of the study, whereby all clinicians, patients and outcome assessors were aware of the transfusion policy, which could lead to selection bias or outcome reporting bias. A rationale and methodology paper has been published (15) and the full protocol is available online (16).

Hospitals were eligible if they had >20 AUGIB admissions monthly; >400 adult beds; 24 hour endoscopy; on-site access to intensive care and surgery; and willing to be randomised to and implement a transfusion policy for all new AUGIB admissions . Eligible participants were new presentations with AUGIB aged ≥18 years; the only exclusion was exsanguinating haemorrhage for which objective guidance criteria were provided (web appendix page 1). Written informed consent was sought from individual participants or their representative for use of routine hospital records and telephone follow up at day 28. Ethical approval was granted in England and Scotland.

Randomisation and Masking

Centres were randomised to a transfusion policy using a random permuted block of six (three hospitals per policy), without stratification or matching. Participants were identified from Emergency Departments and Acute Admissions Units between the 3rd September 2012 and 1st March 2013.

Procedures

In the restrictive policy, participants were eligible for RBC transfusion when the haemoglobin concentration (Hb) fell below 80 g/L, with a post-transfusion target Hb of 81-100 g/L. In the liberal policy, patients were eligible for transfusion when Hb fell

below 100 g/L, with a target post-transfusion Hb of 101-120 g/L. These thresholds were informed by UK transfusion practice during the study design (15). The number of RBC units transfused and the timing of repeat Hb measurements was per clinician discretion. All clinicians could deviate from the policy, but were approached 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 (17-18).

A lead clinician championed the study at each site, supported by a co-investigator from an allied acute specialty. A multi-faceted approach was used to implement the policy including the daily presence of a research nurse in acute areas, regular attendance 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 AUGIB occurred.

Outcome measures

Feasibility and clinical outcome measures were collected. Definitions are available in the online protocol (16). Feasibility outcomes included recruitment rate, adherence to the transfusion policy (overall, per patient, and per Hb count), Hb and RBC exposure and evidence of selection bias. We measured Hb levels (over the first seven days, over the entire follow-up period, and prior to discharge), the proportion of patients receiving at least one RBC transfusion and the number of units transfused. Clinical outcomes were further bleeding, thromboembolic events, and infection (in-hospital and at day 28, with day 28 being the main analysis time point). Mortality, serious adverse events, and the Euroqol EQ-5D questionnaire were assessed at day 28.

Statistical analyses

Based on 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 (19) score between treatment policies, which might indicate selection bias. Using a two-sided significance level of 5%, an intra-cluster correlation coefficient (ICC) of 0·033 and

standard deviation of 1·84, 849 participants would provide 92% power to detect a mean difference of one point (15).

The statistical analysis plan was published before database lock (20). All analyses were pre-defined unless otherwise stated. Analyses were performed on all enrolled patients for whom an outcome was available. We also performed an analysis on all enrolled patients with a Hb below 120g/L during follow-up, as it was anticipated *a priori* this group was most likely to receive a transfusion and be affected by the treatment policy.

Feasibility and clinical outcomes were analysed using cluster-level summaries, with equal weight given to each cluster (21-22). Results are presented as a difference in means for continuous outcomes, and a difference in proportions for binary outcomes. Pre-specified subgroup analyses and *post-hoc* analyses are listed in the web appendix (page 3).

Role of the funding source

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

Results:

Screening and enrolment

There were 1667 AUGIB admissions to the six hospitals during the recruitment period of whom 1600 of 1667 (96%) were eligible and 936 of 1660 (59%) enrolled (Figure 1). Recruitment rate was significantly higher in the liberal policy (62% vs. 55%, p=0·04). Three percent were ineligible due to exsanguinating bleeding (19 of 896 [2%] liberal arm *vs.* 33 of 771 [4%] restrictive arm; p=0·08). The commonest reason for non-enrolment was consent refusal for data collection and telephone follow up which occurred in 430 of 1600 (27%). Data on further bleeding were missing in no patients at hospital discharge, but in 31 of 936 (3%) at day 28 who were excluded from the analysis. Telephone contact at day 28 to administer an EQ-5D questionnaire was not possible in 136 of 403 (34%) participants in the restrictive policy and 296 of 533 (56%) in the liberal policy.

Baseline characteristics and selection bias

Baseline characteristics were similar in terms of Rockall and Blatchford risk scores, blood pressure, heart rate, and symptoms of bleeding (Table 1 and web appendix Table 1). There were some baseline imbalances in co-morbidities with a greater proportion of patients in the liberal policy with liver disease (91 of 533 [17%] *vs.* 45 of 403 [11%]) whereas more patients in the restrictive policy had respiratory disease (84 of 403 [21%] *vs.* 74 of 533 [14%]) or hypertension (123 of 403 [31%] *vs.* 109 of 533 [20%]). The prevalence of ischaemic heart disease (IHD) was the same between treatment arms. Bleeding was due to peptic ulcer disease in 153 of 673 (22%), erosive disease in 171 of 673 (25%) and gastro-oesophageal varices in 81 of 673 (12%). In the liberal policy, patients enrolled were older than those not enrolled, compared to the restrictive policy, where patients enrolled were younger than those not enrolled (Table 2).

Protocol adherence

Overall adherence to the transfusion protocol (mean number of Hb counts with no deviations, per patient) was significantly higher in the restrictive policy (96%; sd 10) compared to the liberal policy (83%; sd 25; p= 0·005), with a similar pattern seen in patients with a Hb <120 g/L (restrictive policy 94% [sd 12] *vs* liberal policy 76% [sd 27]; p=0·003) (Table 3). Adherence each month was consistent in the restrictive policy, but decreased in the liberal policy (Figure 2). In the liberal policy 675 of 2769

(24%) of all Hbs led to a protocol deviation (672 no transfusion administered when Hb<100 g/L; three transfusions administered when Hb>100 g/L), compared with 93 of 1754 (5%) in the restrictive group (67 no transfusion administered when Hb<80 g/L, 26 transfusions administered when Hb>80 g/L).

Transfusion and Hb separation

Amongst all patients, 247 of 533 (46%) were transfused in the liberal policy compared to 133 of 403 (33%) in the restrictive policy (difference -12%, 95% CI -35 to 11, p=0·23). The mean number of units transfused was lower in the restrictive policy (1·2 units [sd 2·1] restrictive policy *vs* 1·9 units [sd 2·8] liberal policy; difference -0·7 units, 95% CI -1·6 to 0·3, p=0·12) (Table 3). In patients with a Hb<120 g/L the Hb at hospital discharge was significantly lower in the restrictive policy (101 g/L [sd 13] restrictive policy *vs* 107 g/L units [sd 12] liberal policy; difference -7 g/L, 95% CI -14 to 0·0, p=0·05) (Figure 3). In the cohort with a Hb <100 g/L, the mean Hb over the entire follow up period as well as at discharge was significantly lower in the restrictive policy compared to the liberal policy (Table 3).

Clinical outcomes

There were no significant differences in clinical outcomes or mean EQ-5D between treatment groups (Table 4). Further bleeding at 28 days (patients with Hb <120 g/L) occurred in 13 of 257 (5%) in the restrictive policy compared to 31 of 383 (9%) in the liberal policy (difference -3·7%; 95% CI -12·2 to 4·8%). Mortality at 28 days (patients with Hb <120 g/L) occurred in 14 of 257 (5%) in the restrictive policy compared to 25 of 383 (7%) in the liberal policy (difference -1·3%; 95% CI -8·0 to 5·5%) (Table 4).).

Discussion

This is the first multi-centre randomised trial comparing transfusion strategies for AUGIB, gathering evidence for the feasibility of a phase 3 trial. The pragmatic eligibility criteria mean that 96% of participants were eligible, of whom almost 60% were enrolled. The cluster design was acceptable to clinicians, resulted in an efficient recruitment rate and facilitated implementation of the transfusion policy hospital-wide, alongside routine clinical care. A high level of 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 Hb. The modest reduction in mean number of RBC units transfused was in keeping with that reported in a meta-analysis of transfusion trigger trials (23).

Protocol adherence was better in the restrictive policy where it was consistent throughout the trial. In the liberal policy most violations were due to not administering RBCs below the threshold of 100 g/L. This greater adherence to the restrictive policy may reflect clinician bias for lower transfusion thresholds for AUGIB, particularly for lower risk patients, extrapolated from evidence of the safety of more 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. Guidelines advocating restrictive transfusion for AUGIB are based upon a single trial conducted in an intensive care population, where patients with acute bleeding were specifically excluded (5); transfusion requirements may reasonably be expected to differ after acute bleeding due to rapid development of anaemia and haemodynamic compromise. For the phase 3 trial, we plan to lower the threshold for transfusion in the liberal arm to reflect this changing practice and we would also exclude lower risk patients (Rockall score = 0) who are unlikely to be transfused.

The greater adherence in the restrictive policy may 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 observed in patients transfused below 70 g/L, compared to 90 g/L. Whether these results would be obtained in other hospitals particularly in the UK is questionable on several grounds. Firstly, a high proportion of the trial population

had liver cirrhosis and variceal bleeding; a treatment effect was only observed in these patients in whom mechanisms of bleeding differ and who account for only 10% of UK presentations with AUGIB. Secondly, the trial excluded patients with major comorbidities including IHD, vascular disease or stroke which excludes almost 40% of all UK presentations with AUGIB (24), representing the group at greatest potential of complications from acute anaemia. Thirdly, processes of care are unlikely to be reproducible at other institutions, specifically the delivery of therapeutic endoscopy to all patients within six hours, which may influence transfusion use. Furthermore, single centre trials tend to find larger treatment effects than multi-centre trials (25), highlighting the risk of making strong recommendations based on a single centre trial (25-26).

Despite some baseline imbalances, participants in each policy had similar risk scores and haemodynamic status. Participants enrolled in the liberal policy were older than those not enrolled, while in the restrictive arm those enrolled were younger than participants not enrolled. These are most likely chance imbalances due to the small number of clusters. For the main trial, approximately 30 clusters would need to be randomised and this is likely to achieve acceptable balance between treatment arms. Pre-specified covariate adjustment will also account for any unexpected baseline imbalances in important prognostic factors (27). It is possible that baseline imbalances were due to selection bias given the open-label nature of the study. Preventing selection bias will be important in the phase 3 trial. A potential solution is to seek consent waiver for anonymous data collection to allow routinely collected data to be summarised on all eligible participants.

TRIGGER was not a phase 3 trial, so its clinical outcomes should not be used to directly inform clinical practice. A key area of uncertainty in transfusion practice concerns safe transfusion thresholds in patients with IHD (8, 10, 28), particularly relevant to AUGIB where 14% have IHD. A pilot trial of transfusion strategies in patients with IHD found a 15% absolute increase in mortality in patients receiving transfusion at a threshold of 80 g/L compared to 100 g/L (10), a similar magnitude of excess mortality as that observed in TRIGGER (web appendix page 4), highlighting the need for further evidence before advocating universal restrictive transfusion for AUGIB.

This feasibility trial provides key learning points for the 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 unlikely to be recipients of transfusion. For higher risk patients with IHD or cerebrovascular disease who may be particularly susceptible to adverse effects of anaemia, we would ask the Independent Data Monitoring Committee to monitor SAEs and provide recommendations at formal interim analysis about their continued enrolment, as well as conducting pre-specified subgroup analysis for IHD. Despite the results of the Barcelona trial (14), we would also enroll patients with liver cirrhosis, given the limitations of external validity in that trial. For the interventions, we plan to lower thresholds for transfusion to 90 g/L in the liberal arm and to 70 g/L in the restrictive arm which accounts for the area of uncertainty in current practice. Whilst previous transfusion strategy trials have used Hb level as an entry criterion (5, 6, 8, 14), we designed this trial to assess the impact of implementing a treatment policy on a hospital wide scale for all patients presenting with AUGIB, and would repeat this efficient design for a phase 3 trial, but additionally incorporate a pre-specified secondary analysis of clinical outcomes using the transfusion threshold in the liberal arm as a cut-off.

The primary outcome for the phase 3 trial would be mortality. Our estimate of the ICC, essential for sample size calculation, was similar to that estimated from a UK audit of AUGIB, likely to reflect that both studies were pragmatic, recording all presentations with AUGIB. We would still randomise by cluster in order to evaluate the treatment effect of a policy in a diverse patient population in routine clinical care, whilst minimising contamination. These benefits far outweigh the commonly cited limitation of statistical inefficiency in cluster 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, recruitment time would be almost 40% less, resulting in a more efficient trial design (web appendix page 5). We believe this design offers an attractive method of conducting comparative effectiveness research in the NHS for treatment policies that are within the boundaries of normal care and where there is clinical equipoise.

Participant consent for routine clinical data and telephone follow up was lower than anticipated. For the phase 3 trial we would seek consent waiver to enable analysis of

routinely recorded in-hospital data on all patients. The trial design would be more efficient through linkage to routine administrative data to record mortality and re-admissions, which would also permit follow up to longer horizons. Telephone follow up at day 28 for patient reported outcomes would be replaced by an assessment of functional status at discharge to reduce attrition rates given difficulties in telephone contact.

Reducing RBC transfusion for AUGIB would have significant financial implications for healthcare agencies. In 2013/14, 1.7 million units of RBCs were issued in England with an estimated 204,000 units for AUGIB alone, costing £123.31 per unit. A 13% reduction, as demonstrated in this trial, would lead to annual savings to the NHS of £3.3m for the blood alone, which excludes blood transfusion laboratory and blood administration costs.

We used a pragmatic cluster randomised design to demonstrate the feasibility of implementing hospital wide transfusion policies for AUGIB, resulting in a reduction in blood use and separation in Hb. Conducting a large cluster-randomised phase 3 trial to assess the effectiveness of transfusion strategies for AUGIB is now essential before practice guidelines are changed to recommend restrictive transfusion for all patients with AUGIB.

PANEL: RESEARCH IN CONTEXT

Systematic review:

We conducted a Cochrane review of randomised controlled trials comparing red cell transfusion strategies for AUGIB in 2008 and updated this in 2010 (29). Three underpowered trials including a total of 93 participants were identified. The small number of participants, missing data and methodological deficiencies did not permit meaningful conclusions, justifying the need for a trial of transfusion strategies for AUGIB. One on-going single centre trial from Barcelona was identified which commenced in 2003 and was published in 2013 (14), half way through TRIGGER recruitment, which reported a reduction in mortality and rebleeding with restrictive transfusion and thus recommended restrictive transfusion for AUGIB. The population in the Barcelona trial differed since one-third had liver cirrhosis where the mechanism of bleeding differs, excluded patients with cardiovascular comorbidity and employed care processes unlikely to be generalisable to most healthcare institutions (3).

Interpretation:

The purpose of TRIGGER was to assess the feasibility and safety of implementing restrictive versus liberal transfusion strategies for AUGIB in UK hospitals using cluster randomisation to inform feasibility of a phase 3 trial. The randomised transfusion policies were successfully implemented on a hospital wide scale across multiple specialty groups and clinical areas for a six month period with a high level of protocol adherence, leading to a reduction in RBC exposure in the restrictive policy and separation in haemoglobin concentration between the treatment groups. No significant differences in clinical outcomes were observed, although the trial was not powered for this. If restrictive transfusion is proven to be safe and effective in a larger, similarly pragmatic trial design, this would have the potential to safely reduce the use of RBCs for the largest single indication for transfusion in England and may have broader implications for the more restrictive use of RBCs after acute haemorrhage. A larger cluster randomised trial is feasible and essential to conduct before clinical practice guidelines recommend restrictive transfusion for all patients with AUGIB.

Table 1: Baseline characteristics, Laboratory parameters and Co-interventions

	Liberal policy (n=533)	**Restrictive policy (n=403)**
Male – no. (%)	322 (60)	244 (61)
Age (years) – mean (SD)	60·4 (20·0)	58·0 (20·3)
Rockall score – median (IQR)	2 (1 to 4)	2 (1 to 4)
Blatchford score – median (IQR)	6 (2 to 10)	6 (1 to 9)
Signs and symptoms		
Melaena – no. (%)	266 (50)	209 (52)
Haematemesis – no. (%)	302 (57)	209 (52)
Heart rate (bpm) – mean (SD)	95·6 (20·1)	94·8 (21·8)
Systolic blood pressure (mmHg) – mean (SD)	125·9 (22·7)	126·9 (22·8)
Pre-existing co-morbidities n(%)		
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 – mean (SD)		
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 Hb during follow up (g/L) – no. (%)		
≤79	146 (27)	118 (29)
80 - 99	146 (27)	69 (17)
100 -120	91 (17)	70 (17)
≥121	149 (28)	146 (36)
Medications and fluids		
Proton pump inhibitor (pre endoscopy) – no. (%)	296 (60)	252 (63)
Iron (oral or IV)* – no. (%)	47 (9)	43 (11)
Any Intravenous fluids**– no. (%)	412 (81)	297 (75)
Colloid volume in 24 hours – mean (SD)	0·2 (0·6)	0·1 (0·4)
Crystalloid volume in 24 hours – mean (SD)	1·6 (1·4)	1·9 (1·7)
Platelets – no. (%)***	13 (2)	13 (3)
Fresh frozen plasma – no. (%)	22 (4)	24 (6)
Cryoprecipitate – no. (%)	1 (<1)	2 (1)
Source of bleeding - no. (%)		
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 missing in 24 patients liberal policy, 11 restrictive policy; **Data missing on 24 patients liberal policy, 8 restrictive policy;*** data missing in 9 cases liberal policy, 1 case restrictive policy for platelets/FFP/cryoprecipitate.

Table 2 – Differences between eligible patients who were enrolled vs. not enrolled

Parameter	Liberal policy			Restrictive policy			
	Enrolled n=533	**Not-enrolled n=363**	**Difference between enrolled vs. not-enrolled**	**Enrolled n=403**	**Not-enrolled n=368**	**Difference between enrolled vs. not-enrolled**	**P-value for difference between treatment policies**
Age (years)	59·9 (20·0)	53·9 (23·4)	5.2	57·4 (20·3)	59·8 (23·6)	-2.6	0·05
Hb 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

*All data presented as a mean (sd). In the liberal policy there were 533 patients enrolled vs. 363 not enrolled, and in the restrictive policy there were 403 patients enrolled vs. 368 not enrolled.

Table 3: Protocol adherence, RBC transfusion and Haemoglobin results[†]

Outcome	Liberal policy	Restrictive policy	Treatment effect* (restrictive vs. liberal) and 95% CI	P-value
All enrolled patients	**n=533**	**n=403**		
Overall adherence %– mean (SD) **	83 (25)	96 (10)	14 (7 to 21)	0·005
Patients receiving at least one transfusion – no. (%)	247 (46)	133 (33)	-12 (-35 to 11)	0.23
Number of units transfused – mean (SD)	1·9 (2·8)	1·2 (2·1)	-0·7 (-1·6 to 0·3)	0·12
Mean Hb over entire follow-up period – mean (SD)	115 (23)	115 (26)	-1·0 (-12·0 to 11·0)	0·90
Last recorded Hb – mean (SD)	118 (20)	116 (24)	-2·0 (-12·0 to 7·0)	0·50
Patients with Hb<120 g/L	**(n=383)**	**(n=257)**		
Overall adherence % – mean (SD)	76 (27)	94 (12)	19 (11 to 26)	0·003
Patients receiving at least one transfusion – no· (%)	246 (64)	132 (51)	-12 (-36 to 12)	0·24
Number of units transfused – mean (SD)	2·6 (3·0)	1·8 (2·5)	-0·8 (-1·9 to 0·3)	0·12
Mean Hb over entire follow-up period – mean (SD)	103 (13)	98 (15)	-5·0 (-13·0 to 3·0)	0·18
Last recorded Hb prior to discharge – mean (SD)	107 (12)	101 (13)	-7·0 (-14·0 to 0·0)	0·05
Patients with Hb<100 g/L	**(n=293)**	**(n=190)**		
Overall adherence %– mean (SD)	69 (28)	93 (14)	24 (16 to 32)	0·001
Patients receiving at least one transfusion – no. (%)	242 (83)	130 (68)	-14·3 (-32·2 to 3·6)	0·09
Number of units transfused – mean (SD)	3·4 (3·0)	2·4 (2·6)	-1·0 (-2·0 to 0·01)	0·05
Mean Hb over entire follow-up period – mean (SD) ***	98 (10)	92 (10)	-0·6 (-11·0 to -1·0)	0·02
Last recorded Hb prior to discharge – mean (SD)****	105 (12)	96 (11)	-9·0 (-14·0 to -4·0)	0·007

*Treatment effects are difference in means for continuous outcomes, and a difference in percentage points for binary outcomes; **Overall adherence refers to the proportion of Hb counts where no deviation from the transfusion policy occurred for each patient; ***18 patients had missing data and were excluded from this analysis (16 Liberal, 2 Restrictive); ****50 patients had missing data and were excluded from this analysis (37 Liberal, 13 Restrictive);

Table 4 – Clinical outcomes (patients with Hb < 120 g/L)

Outcome	Liberal policy (n=383)	Restrictive policy (n=257)	Treatment effect* (restrictive vs. liberal) and 95% CI
Further bleeding – no. (%)			
Day 28	31 (9)	13 (5)	-3·7 (-12·2 to 4·8)
Hospital discharge	24 (6)	9 (4)	-3·3 (-13·4 to 6·9)
All-cause mortality – no. (%)			
Day 28	25 (7)	14 (5)	-1·3 (-8·0 to 5·5)
Thromboembolic or ischaemic events – no. (%)			
Day 28	23 (7)	9 (4)	-3·5 (-9·9 to 3·0)
Hospital discharge	21 (5)	7 (3)	-3·3 (-8·7 to 2·2)
Surgical or radiological intervention – no. (%)			
Hospital discharge	11 (3)	10 (4)	0·9 (-4·2 to 5·9)
Acute transfusion reactions – no. (%)			
Hospital discharge	9 (2)	2 (1)	-1·6 (-3·6 to 0·5)
Therapeutic intervention – no. (%)			
At hospital discharge	144 (38)	81 (32)	-7·1 (-25·1 to 10·9)
Infections – no. (%)			
At hospital discharge	92 (24)	67 (26)	0·8 (-25·3 to 26·9)
Length of hospital stay (days) – median (IQR)			
At hospital discharge	5 (3 to 9)	4 (3 to 7)	-0·7 (-1·6 to 0·3)
EQ-5D – mean (SD)			
Day 28	0·69 (0·32)	0·76 (0·27)	0·07 (-0·10 to 0·23)
Serious adverse events – no. (%)			
Day 28	83 (22)	45 (18)	-4.9 (-22·6 to 12·8)

*Treatment effects are difference in means for continuous outcomes, and a difference in percentage points for binary outcomes;

Missing data: 27 patients had missing data for further bleeding and were excluded from this analysis (19 Liberal, 8 Restrictive); 1 patient was missing day 28 mortality in the liberal arm and excluded from this analysis; 48 patients were missing data on thromboembolic/ischaemic events at day 28 and excluded from this analysis (33 liberal, 15 restrictive); 5 patients were missing data on acute transfusion reactions and excluded from this analysis (3 liberal, 2 restrictive); 31 patients missing information on length of stay and excluded from this analysis (21 liberal, 10 restrictive); 295 patients missing information on EQ-5D at day 28 and excluded from this analysis (214 liberal, 81 restrictive); 1 patient in the liberal arm missing data on SAEs in the liberal arm and excluded from this analysis.

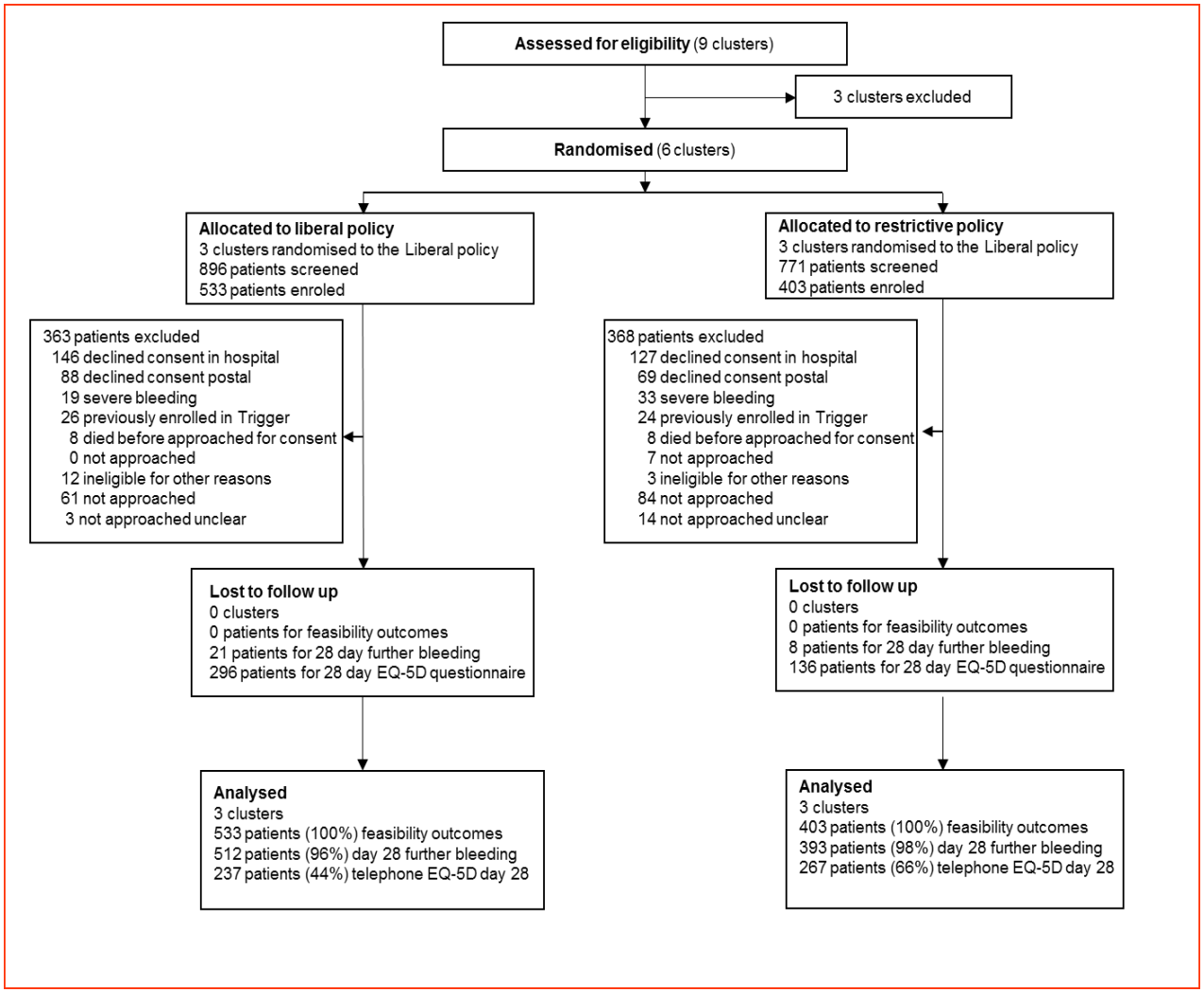

Figure 1 –Trial schema

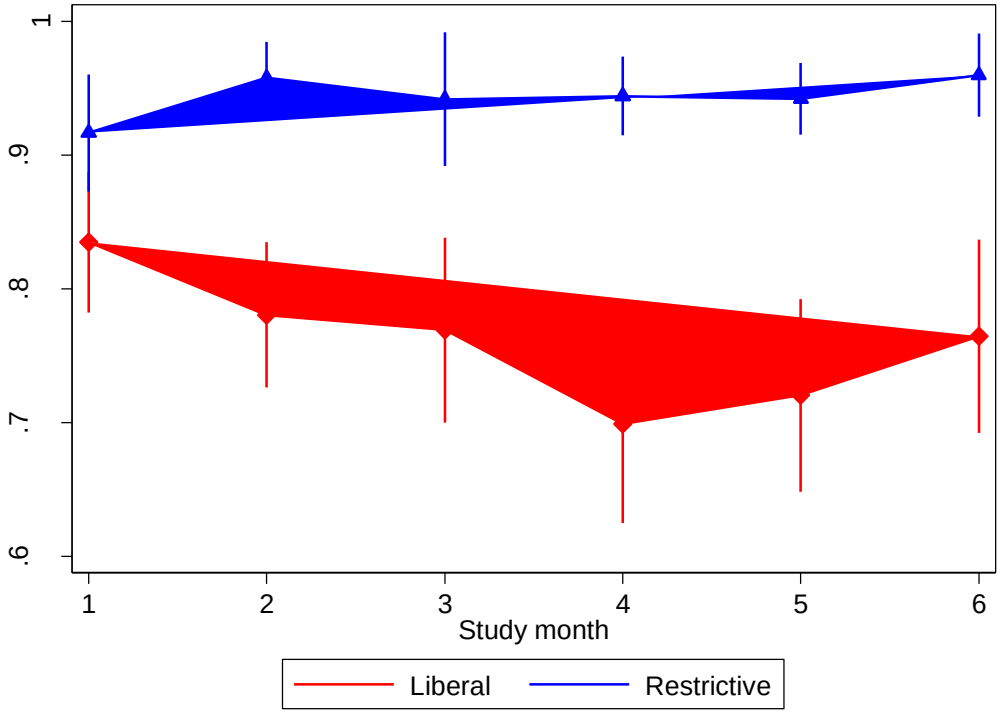

Figure 2 – Overall adherence to the transfusion policy by study month (patients with haemoglobin concentration of less than120 g/L)

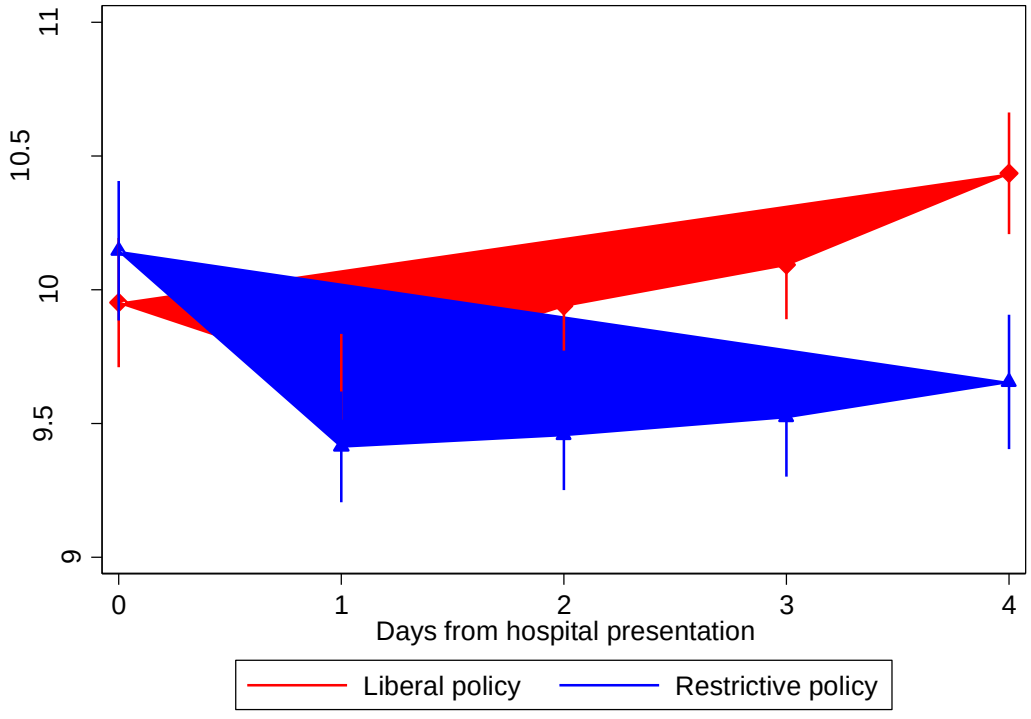

Figure 3 – Mean haemoglobin concentration over time (patients with haemoglobin concentration of less than120 g/L)

Contributors:

VJ – study conception and design, interpretation of data, drafting of manuscript, approval of final version

BCK – study design, analysis and interpretation of data, drafting of manuscript, approval of final version

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Conflicts of interest: We declare that we have no conflicts of interest.

Acknowledgments: The project was funded by NHS Blood and Transplant Research and Development (grant number 10-09-CSU) and run by NHSBT Clinical Trials Unit (formerly NHSBT/ MRC Clinical Trials Unit). The sponsors of the study played no part in the preparation of this article. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of NHS Blood and Transplant. The trial benefited from the support provided by the NIHR Clinical Research Networks. We thank the independent members of the TSC and the IDMC, members of the lay focus group and patient panel who inputted into the trial design and Age UK Abingdon for allowing us to conduct a focus group with members of the public. We thank all clinical teams in participating centres for their support and following the transfusion policies.

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Supplementary Appendix

Guidance criteria used to define ineligibility due to exsanguinating bleeding

1. The patient was prescribed emergency O-negative blood
2. The patient had features of shock (defined as systolic blood pressure <100 mm/Hg and/or heart rate >100 beats per minute) AND was transfused red blood cells within 2 hours of presentation
3. The first endoscopy was performed in the emergency department, HDU/ICU (or equivalent) or operating theatre due to severity of bleeding.

Definition of AUGIB
Haematemesis or the passage of melaena

Table 1: Additional Baseline Characteristics of the patients enrolled

	Liberal arm (n=533)	**Restrictive arm (n=403)**
Time since onset of GI bleed symptoms - no. (%)		
<12 hours	274 (52)	154 (38)
12-24 hours	94 (18)	82 (20)
>24 hours	152 (29)	145 (36)
Not known	12 (2)	22 (5)
Rockall score – median (IQR)	2 (1 to 4)	2 (1 to 4)
Blatchford score – median (IQR)	6 (2 to 10)	6 (1 to 9)
Signs and symptoms		
Fresh blood per rectum – no. (%)	25 (5)	26 (6)
Syncope – no. (%)	42 (8)	36 (9)
Coffee-ground vomitus – no. (%)	135 (25)	157 (39)
First recorded vital signs		
Heart rate (bpm) – mean (SD)	95·6 (20·1)	94·8 (21·8)
Temperature (Celsius) – mean (SD)	36·6 (07·)	36·5 (0·9)
Oxygen saturation (%) – mean (SD)	97·5 (2·2)	97·4 (2·6)
Systolic blood pressure (mmHg) – mean (SD)	125·9 (22·7)	126·9 (22·8)
Respiratory rate (breaths/minute) – mean (SD)	17·7 (3·6)	18·2 (3·9)
First recorded laboratory data		
Haemoglobin (g/dL) – mean (SD)	114 (34)	119 (32)
Platelet count ($x10^9$L) – mean (SD)	259·2 (121·6)	264·2 (129·4)
INR (seconds) – median (IQR)	1·0 (0·9 to 1·2)	1·0 (0·9 to 1·2)
PT (seconds) – median (IQR)	12 (11 to 13)	13 (12 to 15)
APTT (seconds) – mean (SD)	29·0 (7·1)	30·6 (12·6)
Fibrinogen (g/L) – mean (SD)	3·6 (0·9)	3·3 (1·1)
Sodium (mmol/L) – mean (SD)	138 (4)	138 (4)
Potassium (mmol/L) – mean (SD)	43 (0·6)	4·1 (0·7)
Urea (mmol/L) – mean (SD)	10·2 (7·2)	10·0 (7·6)
Creatinine (mmol/L) – mean (SD)	91 (52)	89 (47)
Albumin (g/L) – mean (SD)	36 (8)	38 (7)
Bilirubin (umol/L) – median (IQR)	11 (7 to 20)	10 (6 to 17)
Alkaline Phosphatase (IU/L) – median (IQR)	112 (75 to 185)	93 (68 to 158)
Alkanine Transaminase (IU/L) – median (IQR)	23 (16 to 38)	20 (13 to 35)
Regular medication prior to admission		
Dipyridamole – no. (%)	1 (<1)	1 (<1)
Selective serotonin re-uptake inhibitor – no. (%)	43 (8)	30 (7)
Proton pump inhibitor – no. (%)	193 (36)	100 (25)
Low molecular weight heparin – no. (%)	5 (1)	9 (2)

Care processes

Overall 45 of 482 (9%) of patients in the trial received endoscopy within 6 hours of presentation and 298 of 482 (62%) within 24 hours. More patients in the liberal policy received therapeutic endoscopy compared to the restrictive policy (149 of 533 [28%] *vs.* 85 of 403 [21%]). Transfusion of platelets, fresh frozen plasma and cryoprecipitate was similar between policies.

Other clinical outcomes

There were no significant differences in any clinical outcomes between the two groups. Thromboembolic or ischaemic events were reported in nine of 257 (4%) in the restrictive policy compared to 23 of 383 (7%) in the liberal policy (difference -3·5%; 95% CI -9·9 to 3·0%). Serious adverse events were reported in 45 of 257 (18)% the restrictive policy compared to 83 of 383 (22%) the liberal policy (difference -4·9%; 95% CI -22·6 to 12·8%. In patients with ischaemic heart disease, death was reported in 6 of 49 cases (12%) in the restrictive policy compared to 2 of 67 cases (3%) in the liberal policy (difference 10·7%, 95% CI -9·8 to 31·2; interaction p=0·11).

Table 2: Clinical outcomes – post-hoc adjusted analyses* (Hb<12)

Outcome	Liberal policy (n=383)	Restrictive policy (n=257)	Treatment effect** (restrictive vs. liberal) and 95% CI
Further bleeding			
Day 28	31 (9)	13 (5)	-3·6 (-8·7 to 1·5)
Hospital discharge	24 (6)	9 (4)	-3·0 (-8·7 to 2·8)
All-cause mortality			
Day 28	25 (7)	14 (5)	0·6 (-3·3 to 4·5)
Thromboembolic or ischaemic events			
Day 28	23 (7)	9 (4)	-2·0 (-6·2 to 2·2)
Hospital discharge	21 (5)	7 (3)	-1·8 (-5·2 to 1·6)
Surgical or radiological intervention			
Hospital discharge	11 (3)	10 (4)	0·8 (-3·0 to 4·6)
Acute transfusion reactions			
Hospital discharge	9 (2)	2 (1)	-1·1 (-2·5 to 0·4)
Therapeutic intervention			
At hospital discharge	144 (38)	81 (32)	-5·4 (-14·1 to 3·2)
Infections			
Day 28	92 (24)	67 (26)	4·0 (-28·5 to 36·5)
Length of hospital stay (days)	5 (3 to 9)	4 (3 to 7)	-1·0 (-2·7 to 0·6)
EQ-5D			
Day 28	0·69 (0·32)	0·76 (0·27)	0·02 (-0·13 to 0·18)
Serious adverse events			
Day 28	83 (22)	45 (18)	-2·9 (-13·8 to 8·1)

*Analyses are adjusted for age, heart rate, systolic blood pressure, respiratory rate, Hb, time since onset of symptoms, haematemesis, suspected active bleeding, syncope, suspected shock, ischaemic heart disease, respiratory disease renal disease, liver disease, cancer, PPI, and coagulation

**Treatment effects are difference in means for continuous outcomes, and a difference in percentage points for binary outcomes.

Table 3: Presumed cause of death up to day 28 (all patients)

	Liberal arm (n=26 deaths)	**Restrictive arm (n=16 deaths)**
Presumed cause of death – no. (%)		
Cardiac failure	2 (8)	1 (7)
Liver failure	4 (15)	1 (7)
Malignancy	6 (23)	2 (13)
Multi-organ failure	1 (4)	0 (0)
Other	8 (31)	5 (33)
Respiratory failure	2 (8)	1 (7)
Uncontrolled bleeding	2 (8)	1 (7)
Unknown	1 (4)	4 (27)

Pre-specified adjusted analyses

Main analyses were unadjusted for baseline covariates, however a pre-specified secondary analysis for clinical outcomes was performed after adjustment for age, shock, coagulopathy, and the number of major co-morbidities. Mean imputation was used to account for missing baseline covariates, and age and the number of major co-morbidities were modelled using fractional polynomials.

Pre-specified subgroup analyses conducted

Pre-specified subgroup analyses were performed using an interaction test for further bleeding and all-cause mortality at day 28 for presence *vs.* absence of ischaemic heart disease and for variceal *vs.* non-variceal bleeding

Post-hoc analyses conducted

Analyses conducted *post-hoc* were: (a) adherence, Hb, and transfusion outcomes on patients with a recorded Hb below 100 g/L; (b) adherence outcomes on patients with variceal bleeding and (c) clinical outcomes adjusting for more baseline covariates to account for imbalances

Full list of baseline covariates adjusted for

Age, heart rate, systolic blood pressure, respiratory rate, Hb, time since onset of symptoms, haematemesis, suspected active bleeding, syncope, suspected shock, ischaemic heart disease, respiratory disease renal disease, liver disease, cancer, use of proton pump inhibitors and presence of coagulopathy (INR>1.5).

Updated estimates of the ICC

The updated ICC estimate from these trial data were calculated as 0.026 for further bleeding and 0.001 for mortality. These were almost identical to the estimates from observational data before the trial was conducted (0.027 for further bleeding and 0.001 for mortality) (15).

Table 4: Subgroup analyses (patients with Hb < 12)

Outcome	Subgroup	Liberal arm – no. (%) with outcome	Restrictive arm – no. (%) with outcome	Treatment effect* (restrictive vs. liberal) and 95% CI	P-value for interaction
Ischaemic heart disease					
Further bleeding	No	25/298 (8)	10/203 (5)	-3·9 (-12·1 to 4·4)	0·85
	Yes	6/66 (9)	3/46 (7)	-2·7 (-20·8 to 15·4)	
Mortality	No	23/315 (7)	8/208 (4)	-3.2 (-8·4 to 1·9)	0·11
	Yes	2/67 (3)	6/49 (12)	10·7 (-9·8 to 31·2)	
Variceal bleeding**					
Further bleeding	No	23/259 (9)	9/195 (5)	-4·5 (-9·2 to 0·3)	0·73
	Yes	7/51 (14)	4/22 (18)	0·7 (-40·2 to 41·6)	
Mortality	No	12/268 (4)	10/198 (5)	0·4 (-7·1 to 8·0)	0·18
	Yes	6/55 (11)	1/23 (4)	-7·1 (-20·3 to 6·0)	

*Treatment effects are difference in percentage points

**263 patients were missing information on whether they experienced variceal bleeding, and were excluded from the analysis

Design features of the proposed main trial based upon learning points from TRIGGER

Population

Inclusion criteria: All new adults presenting with AUGIB, defined of haematemesis or passage of melaena.

Exclusion criteria: Patients with exsanguinating bleeding; those with a Rockall score of zero at presentation to hospital; existing in-patients who develop bleeding.

Interventions

Restrictive transfusion policy: Eligible for transfusion if Hb <70 g/L, with a post-transfusion target of 70-90 g/L

Liberal transfusion policy: Eligible for transfusion if Hb < 90 g/L, with a post-transfusion target of 90-110 g/L

As per the feasibility study, the timing and frequency of Hb measurements, as well as the number of units transfused, will not be protocolised. This will enhance the generalisability of the study and the relevance to routine clinical care.

Outcomes

Primary outcome: Mortality within 28 days after presentation. Cause specific mortality will also be recorded.

Mortality and hospital re-admission data will also be sought 12 months after enrolment. For deaths, NHS information centre service will be used to identify the date and cause of death. For re-admissions the NHS Information Centre Trusted Data Linkage service will be used to provide a data-set of patients linked to Hospital Episode Statistics dataset, to include reasons for admission, diagnoses and procedures.

Secondary outcomes will be further bleeding; need for therapeutic intervention; thromboembolic/ischaemic events; infections; transfusion reactions; length of stay; functional status using the Katz Index of Independence in Activities in Daily living at discharge from hospital or in-hospital at 28 days after enrolment (bathing, dressing, toileting, transferring, continence and feeding); patient status at 12 months (death, hospital admission).

Study design

Parallel group, cluster randomised trial, without matching or stratification.

Sample size comparisons between an individually randomised vs. cluster randomised trial

To detect a difference in mortality of 7% vs. 4.5% between treatment groups with 90% power and a two-sided 5% significance level, an individually randomised trial would require 3642 patients. A cluster-randomised trial with 30 clusters and an intraclass correlation coefficient of 0.001 would require approximately 4200 patients (a 15% increase). Assuming that 40 eligible patients present to each month to each of the 30 centres (based upon feasibility trial results), and that 40% of eligible patients are enrolled in an individually randomised trial compared to 75% for a cluster randomised trial, an individually randomised trial would complete recruitment in 7.6 months, compared to 4.7 months for a cluster randomised trial (a 38% reduction). These figures do not account for staggered site set up and total trial duration.

Pre-specified subgroup analyses and rationale:

1. Patients with ischaemic heart disease. There is uncertainty as to the optimal management of anaemia in this subgroup, who may be particularly susceptible to the effect of anaemia.
2. Patients with liver cirrhosis and variceal bleeding. Portal hypertensive bleeding has a different aetiology and mechanism of bleeding; this group may be particularly susceptible to the effects of volume overload so assessing a treatment effect in this subgroup is important and has biological plausibility
3. Age of blood: mortality (the primary endpoint) in patients transfused blood <7 days of age versus those receiving blood >7 days of age. There is some evidence to suggest harmful effects of older blood, so again a biological plausible subgroup.

Advantages and disadvantages of randomising by cluster for the main trial

Advantages

1. Assess the population level impact of implementing a treatment policy in routine clinical care, which is more useful to patients, clinicians, and healthcare agencies.
2. Ensures a majority of eligible patients are enrolled which enhances the generalisibilty of the results. This is in contrast with previous individually randomised transfusion trials, where as few as 15% of eligible participants are have been enrolled.
3. This is a trial of an acute medical emergency where an intervention has to be implemented immediately at the "front door" and then be maintained as the patient moves across several clinical areas and clinical teams in a short space of time. Cluster randomisation ensures that *all* hospital personnel will be aware of the transfusion policy and can implement it for every patient admitted with AUGIB, ultimately reducing contamination between two differing treatment polices in the same hospital.

Disadvantages

1. Statistical inefficiency and the need for a greater number of patients to be enrolled compared to an individual patient randomised trial. However, we have demonstrated from the rapid recruitment in TRIGGER that recruitment of sufficient participants would not be a limiting factor in this trial.
2. The need for an accurate estimate of the ICC to inform sample size considerations. For the main trial we now have estimates both from the pilot and observational audit, which concur.
3. Lack of blinding as all personnel in a cluster (hospital) would be aware of the transfusion policy, which could lead to biases in outcome reporting, particularly for more subjective outcomes. For the main trial we are using an objective primary endpoint (mortality), so assessment of this endpoint would not be influenced by lack of blinding.