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New, H.V., Sanderson, E., Hopkins, V. et al. (2025) How low can we go? Comparison of liberal and restrictive red cell transfusion thresholds in paediatric allogeneic haematopoietic stem cell transplantation: a randomized multicentre feasibility trial. British Journal of Haematology, 206 (6). pp. 1719-1729. ISSN: 0007-1048

https://doi.org/10.1111/bjh.20051

Received: 1 November 2024 | Accepted: 6 March 2025

DOI: 10.1111/bjh.20051

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Transplantation and Cellular Therapy

How low can we go? Comparison of liberal and restrictive red cell transfusion thresholds in paediatric allogeneic haematopoietic stem cell transplantation: A randomized multicentre feasibility trial

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Funding information
NHS Blood and Transplant Trust Fund, Grant/Award Number: TF070

Summary

Optimal red blood cell transfusion thresholds for children with bone marrow failure are uncertain; a previous study was stopped following concerns about veno-occlusive disease. The aims of this study in allogeneic haematopoietic stem cell transplant (HSCT) were to assess feasibility of recruitment and protocol adherence (primary outcomes) for different haemoglobin (Hb) transfusion thresholds, and to describe safety and present exploratory data on quality of life (QoL). Children aged ≥1 to <18 years were randomized to restrictive Hb transfusion thresholds of 65 g/L (restrictive) vs. 80 g/L (liberal) for HSCT days 0–100. Thirty-four patients were randomized at four UK HSCT centres, 17 in each arm. 48.6% (34/70) of eligible patients were recruited (target ≥50%), with high levels of protocol adherence: % (*n*/*N*) [95% CI] in the restrictive and liberal arms were 99.2 (961/969) [98.6, 99.7] and 97.2 (1131/1164) [96.2, 98.1] respectively (target ≥70% each arm). The mean pre-transfusion Hb was 16.3 g/L higher in the liberal than in the restrictive arm. Feasibility to measure QoL was demonstrated with no evidence of more fatigue in the restrictive arm. Although the study was not powered for clinical outcomes, the findings suggest that some populations may be able to safely tolerate anaemia levels below 70 g/L, the most common restrictive transfusion threshold.

KEYWORDS
haemoglobin threshold, HSCT, paediatric transfusion

INTRODUCTION

In the United Kingdom (UK), the recent infected blood inquiry[1] has reiterated the importance of understanding harm related to blood transfusions, a biological agent. Trial evidence to inform when to transfuse anaemic children, given both risks and benefits,[2,3] is dominated by the findings of one threshold randomized trial in the setting of paediatric intensive care (PICU).[4] This trial recruited around 20 years ago, did not distinguish children with underlying bone marrow failure due to cancer/haematopoietic stem cell transplant (HSCT) nor include quality of life (QoL) outcomes. The only completed trial in children with cancer is a small randomized controlled trial (RCT) in paediatric HSCT which compared Hb thresholds of 120 vs. 70 g/L but only enrolled six patients given an imbalance of veno-occlusive disease (VOD).[5] Although a (restrictive) threshold of 70 g/L is often considered standard for many patient populations (outside neonates), children and young adults are likely to safely tolerate lower Hb thresholds. A large transfusion trial in children with uncomplicated severe anaemia due to malaria recruited once the Hb was below 60 g/L,[6] and a recent trial in asymptomatic young adults following orthopaedic trauma compared Hb transfusion thresholds of 55 vs. 70 g/L.[7]

With this background, a feasibility parallel RCT, with a restrictive arm below 70 g/L, was planned in paediatric allogeneic HSCT to assess recruitment and adherence to the protocol, describe safety and present data on relevant QoL outcomes.

METHODS

Study participants

Eligible patients at the four study sites were children planned to undergo allogeneic HSCT, aged ≥1 and <18 years at consent, anticipated to require red blood cell (RBC) transfusions. Exclusion criteria were: (1) children judged by their clinician inappropriate to be allocated to either study arm, (2) HSCT for haemoglobinopathy or red cell aplasia. Feedback from parents and the public was taken into account during protocol development. Participants were randomized prior to Day 0 of HSCT (D0 of study) in a 1:1 ratio stratified by site. The study was unblinded. Safety reporting included adverse events related to transfusion (Supplementary Methods).

Transfusion policies

Participants were randomized to one of two Hb transfusion thresholds for the study period (HSCT D0 to D100), either Hb ≤65 g/L (restrictive) or ≤80 g/L (liberal; Figure 1). RBC transfusion volume (mL/kg) was calculated to achieve a Hb rise of 20 g/L (8 mL/kg) above the threshold, a maximum of one adult-sized RBC unit unless symptomatic (2 units for outpatients). The protocol applied for inpatient and outpatient transfusions at study centres (Supplementary Methods). The Hb thresholds for this trial were informed by UK audit data that reported a median (IQR) pre-transfusion Hb of 74 g/L (67–80),[8] similar to a Canadian oncology centre Hb of 72 g/L (68–76).[9]

Data collection

Baseline clinical characteristics collected were age at consent, sex, HSCT indication, type and conditioning (ablative vs. non-ablative). Height, weight, comorbidity details (using an HSCT co-morbidity score modified for paediatrics)[10] and any record of red cell alloimmunization were obtained on the admission day for HSCT.

Inpatient data recorded daily were platelet transfusions, major bleeding (modified WHO grading), thromboembolic/ischaemic events, acute transfusion reactions. HSCT toxicity scored was acute graft-versus-host disease (aGvHD, highest grade by D100), modified Bearman toxicity (collated weekly and at discharge up to D28, with analysis of maximum scores)[11] and veno-occlusive disease (VOD, presence/absence within the first 21 days of HSCT; modified Seattle criteria)[12]; see Supplementary Methods.

Outpatient Hb and transfusions were collected post-discharge, and summary data on death, aGvHD and VOD at D100. The length of initial inpatient stay from D0 was not explicitly collected but estimated using the number of days, from randomisation, of continuous reporting of inpatient Hb measurements.

Quality of life

QoL assessments using the Behavioural, Affective and Somatic Experiences Scale (BASES) tool[13,14] were at consent, weekly from D7 for inpatients and D100. In addition, the activity-related question (Q21) was asked daily when inpatient. The parent tool was used for parents, and the patient tool for participants from the age of 8 years. QoL data collection was recommenced if a participant was re-admitted to a participating site.

Outcomes

The two primary outcomes were (1) the percentage of eligible patients recruited and randomized (target at least 50%), (2) adherence to the protocol measured as the percentage of Hb measurements where appropriate action was taken in accordance with the randomized policy, with a target of at least 70% adherence demonstrated at a 5% significance level. Secondary adherence and clinical outcomes

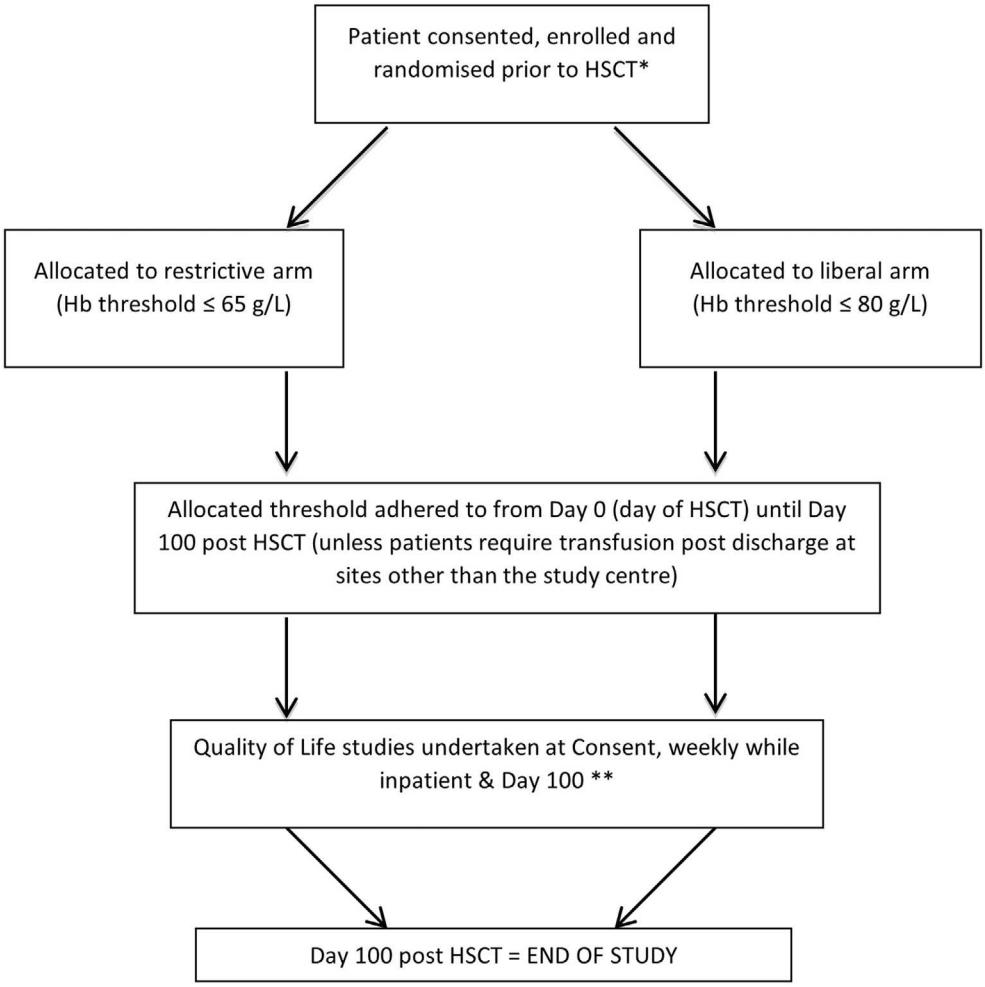

FIGURE 1 Study scheme. *HSCT: Haematopoietic stem cell transplant; **The BASES QoL question 21 was recorded daily while inpatients.

included transfusion, Hb and HSCT toxicity outcomes (Supplementary Methods).

Statistical considerations

This was a feasibility study, and formal sample size calculation was not performed. A sample size of 34 patients randomized (17 in each arm) allowed estimation of the anticipated adherence rate of 70% in each arm with a 95% confidence interval of ±5%, allowing for a participant drop-out rate of 10% and an average of 28 Hb measurements per participant. Estimates for the adherence rate overall would have a 95% confidence interval of ±3% (Supplementary Methods).

The primary recruitment outcome included all patients who were eligible for the study. Secondary measures of feasibility at a patient level and clinical outcomes were analysed in an intention-to-treat analysis, with all randomized participants analysed in their allocated arm. Participants randomized in error, lost to follow up or withdrawn (unless withdrawal of consent for the use of data) were included in this analysis, regardless of whether they had at least one Hb measurement or received at least one transfusion.

RESULTS

Patient recruitment, protocol deviations and data quality

Thirty-four of 70 eligible patients were randomized from four sites over 20 months, 17 to each arm (Figure 2). Fourteen participants in the restrictive and 16 in the liberal arm reached D100. Four discontinued the study (all by D7), three in the restrictive and one in the liberal arm. A further participant in the restrictive arm discontinued treatment but continued in the study. Observations post-withdrawal were not included. All 34 participants contributed data for the primary analysis. During the study, there were six protocol temporary suspensions for five participants, all in the restrictive arm, spanning a total of 17 days.

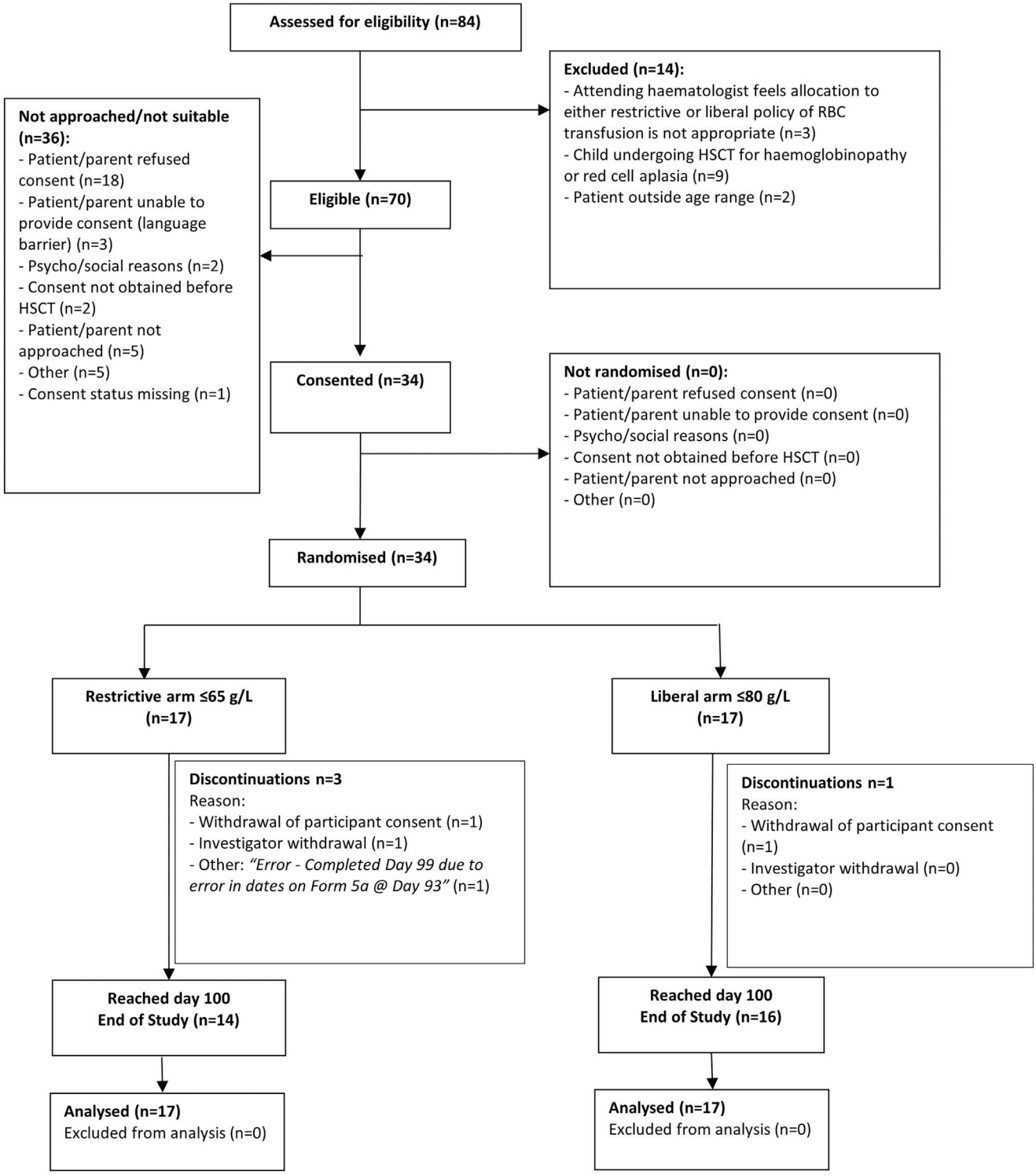

FIGURE 2 CONSORT diagram.

Five suspensions were for protocol-listed reasons; one was pre-bronchoscopy.

Trial data quality was generally very good: primary and secondary outcomes had very low levels of missing data. QoL outcomes were patient-reported (child and parent) and less complete, with 46.2% of expected data missing for children and 25.7% for parents.

Baseline characteristics

Median age was 7 years in both arms (overall IQR 4–11 years). Baseline characteristics were generally balanced between arms: most children received myeloablative HSCT, although more in the restrictive versus liberal arm had an underlying diagnosis of acute myeloid

TABLE 1 Baseline characteristics of participants.

	Restrictive ≤65 g/L (*n* = 17)	Liberal ≤80 g/L (*n* = 17)	Total (*n* = 34)
Male	11 (64.7)	9 (52.9)	20 (58.8)
Age (years)	7 (3, 11)	7 (5, 10)	7 (4, 11)
Height (cm)	126 (94, 141)	121 (112, 141)	123.5 (99, 141)
Weight (kg)	27.6 (13.9, 30.0)	29.0 (21.1, 37.7)	27.7 (17.8, 37.7)
Diagnosis			
ALL	2 (11.8)	10 (58.8)	12 (35.3)
AML	8 (47.1)	2 (11.8)	10 (29.4)
Other leukaemia	2 (11.8)	1 (5.9)	3 (8.8)
Neuroblastoma	0	0	0
Other solid tumour	0	0	0
Non-malignancy[a]	5 (29.4)	4 (23.5)	9 (26.5)
Type of transplant			
Matched sibling	0	5 (29.4)	5 (14.7)
Matched unrelated	10 (58.8)	10 (58.8)	20 (58.8)
Mismatched	1 (5.9)	0	1 (2.9)
Cord blood HSCT—Matched	4 (23.5)	0	4 (11.8)
Cord blood HSCT—Mismatched	2 (11.8)	2 (11.8)	4 (11.8)
Haploidentical	0	0	0
Chemotherapy conditioning type			
Ablative	13 (76.5)	16 (94.1)	29 (85.3)
Non-ablative	4 (23.5)	1 (5.9)	5 (14.7)
HCT comorbidity total score	0.0 (0.0,0.0)	0.0 (0.0, 0.5)	0.0 (0.0,0.0)
Positive red cell alloantibodies	0	0	0

Note: Baseline characteristics data are number (%) for categorical variables and median (interquartile range) for continuous variables. Missing data: One observation missing for HCT comorbidity total score in the liberal arm.

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; HCT, Hematopoietic Cell Transplantation; HSCT, haematopoetic stem cell transplant.

[a]Non-malignancy diagnoses: Restrictive arm—very severe aplastic anaemia (hepatitis associated), severe aplastic anaemia (2), inherited bone marrow failure syndrome (2; 1 with short telomeres, 1 with biallelic mutation of DNAJC21); liberal arm—Fanconi Anaemia with progressive bone marrow failure, myelodysplastic syndrome (reported as non-malignancy), Noonan syndrome with monosomy 7, mucopolysaccharidosis type 1.

leukaemia (AML, 58.8% vs. 11.8%; Table 1). Median (IQR) length of initial inpatient stay (from D0) was 44.5 (33, 65) days; 44.5 (35, 66) in the restrictive and 46 (31, 63.5) in the liberal arm, excluding withdrawals during the initial inpatient stay.

Primary outcomes: Percentage of eligible patients randomized and adherence to study protocol

The first primary outcome for the trial was the percentage of eligible participants recruited and randomized. At 48.6% (34/70), the study was just below the feasibility target (50%). The second primary outcome, adherence, was the percentage of Hb measurements where appropriate action was taken in accordance with the randomized policy. There was strong evidence (*p*-values <0.0001) that overall adherence in each arm was above the 70% target. Adherence (% (*n*/*N*) [95% CI]) in the restrictive and liberal arms was 99.2 (961/969) [98.6, 99.7] and 97.2 (1131/1164) [96.2, 98.1] respectively (Table 2). For measurements of Hb at or below threshold, transfusions were given on 48/51 (94.1%) occasions in the restrictive arm but only on 67/97 (69.1%) in the liberal arm, suggesting less strict protocol adherence in the liberal arm.

Per protocol/sensitivity analyses

Sensitivity analysis was performed to account for missing primary outcome data for protocol adherence. There were only three occasions where an Hb measurement was missing when indicated. The per protocol cohort included 27 patients who were compliant to the transfusion strategy at least 80% of the time, had at least one Hb measurement and were not randomized in error, lost to follow up, withdrawn or experienced a protocol deviation. Sensitivity and per-protocol analyses gave very similar results to the primary analysis.

TABLE 2 Primary outcome: Adherence to protocol.

	Restrictive ≤65 g/L (*n* = 17)		Liberal ≤80 g/L (*n* = 17)		Total (*n* = 34)	
Hb measurements	**Trfs given[b]**	**Trfs not given**	**Trfs given[b]**	**Trfs not given**	**Trfs given[b]**	**Trfs not given**
Hb measurement at or below threshold *n*/*N* (%)[a]	**48/51 (94.1)**	3/51 (5.9)	**67/97 (69.1)**	30/97 (30.9)	**115/148 (77.7)**	33/148 (22.3)
Hb measurement above threshold *n*/*N* (%)[a]	5/918 (0.5)	**913/918 (99.5)**	3/1067 (0.3)	**1064/1067 (99.7)**	8/1985 (0.4)	**1977/1985 (99.6)**

Hb measurements where appropriate action was taken (*n*) as a proportion of total Hb measurements (*N*)			
	Restrictive ≤ 65 g/L (*n* = 17)	**Liberal ≤ 80 g/L (*n* = 17)**	**Total (*n* = 34)**
n/*N* (%) overall	961/969 (99.2)	1131/1164 (97.2)	2092/2133 (98.1)
Median (IQR) percentage per participant	100 (98.6, 100)	98.7 (97.6, 100)	100 (98.1, 100)
95% CI for % adherence	(98.6, 99.7)	(96.2, 98.1)	(97.5, 98.7)
p-value for one-sided one-sample proportion test against hypothesized value of 70%	<0.0001	<0.0001	

Note: Excludes Hb measurements not at participating hospitals, observations within a suspension of protocol and observations after withdrawal (these exclusions consisted of 293 observations in total). Numbers in bold highlight where appropriate action was taken in accordance with randomised policy.

Abbreviations: Hb, haemoglobin; Trfs, transfusions.

[a]Here, the denominator is the total number of Hb measurements for each arm and threshold category (i.e. at or below vs. above) and the percentage calculated from this. Where the sample warranted a prompt repeat (within 24 h), only the trigger Hb was included in the analysis.

[b]Transfusions must have happened within 24 h of the Hb measurement for inpatients and 72 h for outpatients.

Secondary outcomes for transfusion and Hb levels

Red cell transfusions

The total number of transfusions was 159; 65 in the restrictive and 94 in the liberal arm (Table 3), median per participant 3 in each arm. Only 14/17 participants in the restrictive arm received a transfusion, but two of these non-transfused participants withdrew by D5 (Figure 3). All 17 in the liberal arm were transfused; two received 24 transfusions each. 75.4% (49/65) of transfusions in the restrictive and 72.3% (68/94) in the liberal arm were given according to Hb threshold policy.

Hb levels

A total of 2133 Hb measurements were recorded (Table 2), median per participant 73 in the restrictive arm and 72 in the liberal arm (Table 3). Towards the end of the study, when the majority of children were outpatients, the number of Hb measurements was lower (Figure 4). The mean daily Hb levels appeared similar between arms by D45, by which point 10/14 (71%) in the restrictive arm and 12/17 (71%) in the liberal arm had ceased transfusions.

Mean overall Hb to D100 was 90.1 g/L in the restrictive arm versus 97.6 g/L in the liberal arm, a difference in means of 7.5 g/L (Table 3). Pre-transfusion mean Hbs were consistent with study protocol arms, with a difference between means of 16.3 g/L. The difference between arms for pre-transfusion Hb was noted throughout the study (not shown). Mean post-transfusion Hb in the restrictive arm was above the protocol target Hb of 85 g/L, and in the liberal arm, it was below the target Hb of 100 g/L, with a smaller difference in means of 6.2 g/L.

For red cell transfusions given when the Hb measurement indicated a transfusion according to policy (target Hb should have been according to protocol), 54.2% (26/48) in the restrictive arm and 68.1% (49/72) in the liberal arm were given at the correct dose (volume). Transfusions in the restrictive arm had a higher median (IQR) volume (mL/kg) compared to the liberal arm: 10.0 mL/kg (8.2, 13.6) vs. 8.3 (4.8, 11.5) (Table S1). Moreover, where the dose transfused was incorrect, in the restrictive arm, it was over target for 14 and under for 8; in the liberal arm, it was over for 6 and under for 17 (two had missing volumes). For transfused participants, the median number of red cell units and transfusion episodes per participant was slightly higher in the restrictive arm versus the liberal arm.

Overall, three participants in each arm required an additional transfusion within 24 h of a primary transfusion, resulting in three additional transfusions in the restrictive arm and 15 in the liberal arm (Table S1).

Other clinical secondary outcome measures

There were no deaths reported in either arm (Table S1). There were four WHO grade 3/4 bleeds (3 participants, restrictive arm; 2 lower gastrointestinal bleeding and 2 epistaxis in the same participant; all requiring

TABLE 3 Secondary adherence outcomes: Haemoglobin measurements and transfusions.

	Restrictive ≤65 g/L (*n* = 17)	Liberal ≤80 g/L (*n* = 17)	Total (*n* = 34)
Transfusion policy adherence for enrolled participants			
Number of Hb measurements per participant, median [IQR] (range)[a]	73 [47, 80] (3116)	72 [63, 84] (8, 113)	72.5 (3116)
Number of transfusions per participant, median [IQR] (range)	3 [2,4] (0, 12)	3 [3,4] (1, 24)	3 (0, 24)
Participants who successfully followed the policy *n*/*N* (% of participants)			
100% of the time[b]	2/17 (11.8)	1/17 (5.9)	3/34 (8.8)
80% of the time[b]	14/17 (82.4)	14/17 (82.4)	28/34 (82.4)
RBC transfusions given in accordance with policy, *n*/*N* (% of transfusions)	49/65 (75.4)	68/94 (72.3)	117/159 (73.6)
Percentage of transfusions per participant given in accordance with policy, median (IQR)	66.7 (50, 100)	100 (80, 100)	100 (50, 100)
Red cell transfusions			
Number of participants who received at least one RBC transfusion, *n*/*N* total participants (%)	14/17 (82.4)	17/17 (100%)	31/34 (91.2)
Total number of RBC transfusions throughout trial	65	94	159
RBC transfusions given when Hb measurement indicated that a transfusion was required by policy, *n*/*N* all RBC transfusions (%)	49/65 (75.4)	73/94 (77.7)	122/159 (76.7)
RBC transfusions where the dose was correct[c]	26	50	76
RBC transfusions where the dose was correct of those transfusions required by the policy *n*/*N* (%)	26/48 (54.2)	49/72 (68.1)	75/120 (62.5)
Hb difference			
Hb concentration (g/L) up to day 100, mean (SD)			
Pre-transfusion	63.8 (6.2)	80.1 (13.6)	73.4 (13.8)
Post-transfusion	89.8 (17.4)	95.9 (19.2)	93.4 (18.7)
Overall	90.1 (18.5)	97.6 (16.5)	94.1 (17.8)
Mean difference between trial arms for Hb concentration (g/L), (95% CI for mean)			
Pre-transfusion	−16.3 (−19.5, −13.2)		
Post-transfusion	−6.2 (−12.0, −0.4)		
Overall	−7.5 (−8.9, −6.0)		
Pre-transfusion Hb concentrations falling at or below, or above threshold Hb[d]			
At or below threshold Hb, *n*/*N* pre transfusion measurements (%)	48/65 (73.9)	73/94 (77.7)	121/159 (76.1)
Above threshold Hb, *n*/*N* pre-transfusion measurements (%)	17/65 (26.2)	21/94 (22.3)	38/159 (23.9)
Post-transfusion Hb concentrations falling at or below, or above the target Hb[e]			
At or below target Hb, *n*/*N* post transfusion measurements (%)	28/65 (43.1)	51/94 (54.3)	79/159 (49.7)
Above target Hb, *n*/*N* post transfusion measurements (%)	37/65 (56.9)	43/94 (45.7)	80/159 (50.3)

Note: Excludes samples which warranted prompt repeat.

Abbreviations: Hb, haemoglobin; RBC, red cell.

[a]Excluding withdrawals, all participants had daily Hb results reported for the first 25 days.

[b]Including observations after withdrawals.

[c]Missing transfusion volumes for three observed transfusions (two of which were transfusions required by policy).

[d]The threshold for the restrictive arm is a Hb ≤65 g/L and for the liberal arm ≤80 g/L.

[e]The target for the restrictive arm is a Hb 85 g/L and for the liberal arm 100 g/L.

transfusion). One thromboembolic event was reported (liberal arm). There were two admissions to PICU (restrictive arm).

Bearman toxicity scores were similar across arms: median (IQR) in restrictive and liberal of 3 (2, 6) and 4 (2, 5) respectively. The total number experiencing aGvHD was lower in the restrictive arm: 7/17 (41.2%) compared to the liberal 10/16 (62.5%), as was the grade of aGvHD: 4/17 (23.5%) grade II–IV in the restrictive arm versus 8/16 (50%) in the liberal arm. Of those with aGvHD, the duration with the highest grade per participant was a median (IQR) of 16 (11, 36) days in the restrictive arm versus 24 (12, 38) in the liberal. Occasions of VOD were similar between arms, two within the first 21 days in both arms.

All participants received a platelet transfusion, with a higher median number per participant in the restrictive arm compared to the liberal arm: 7 versus 5. No transfusion-related reactions were reported.

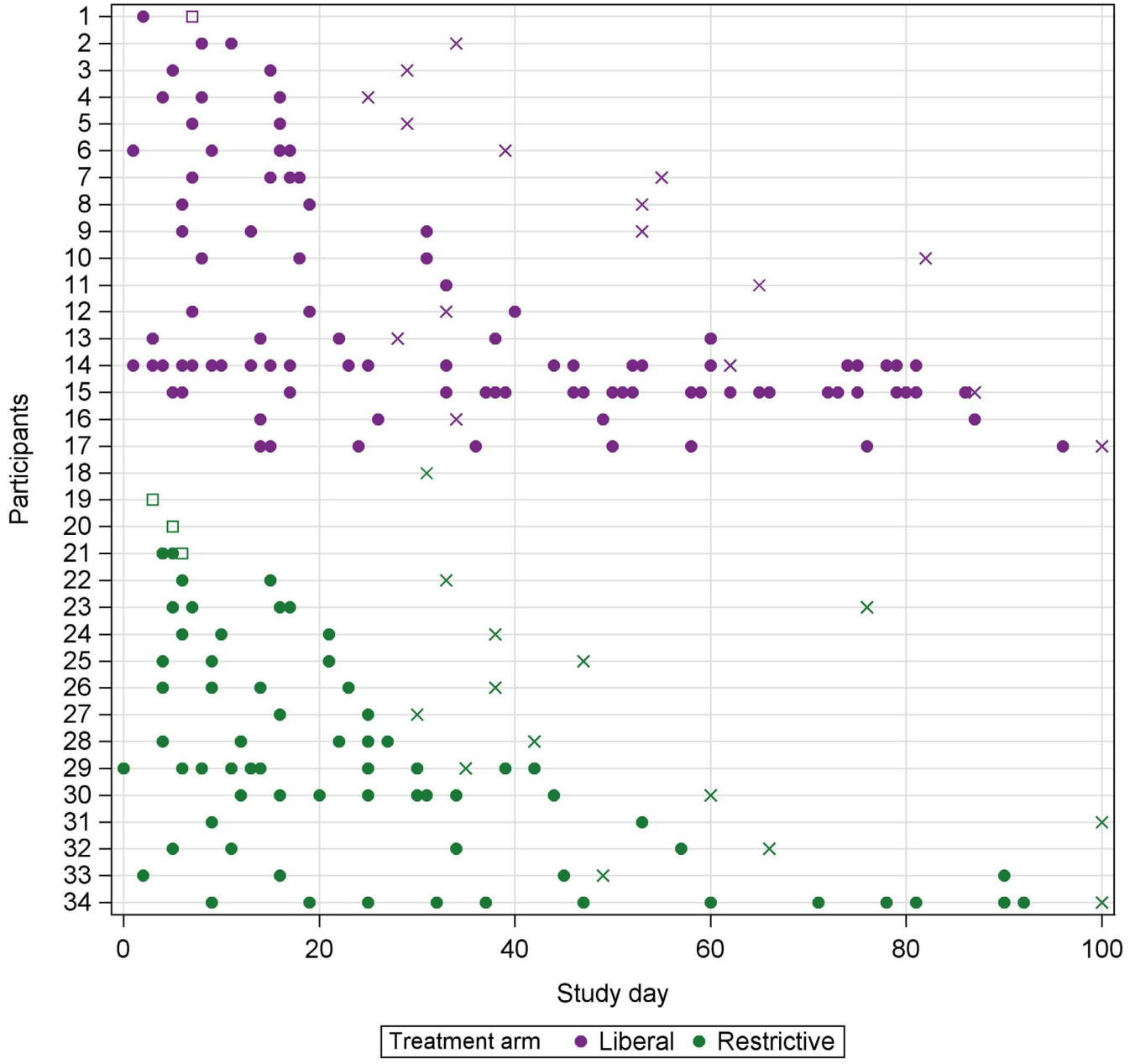

FIGURE 3 Transfusion by time and study arm. Each row represents a participant. Three patients in the restrictive arm did not receive any transfusions.

Quality of life

Overall, there was no difference between arms for any of the five QoL domains (Somatic distress, Compliance, Mood disturbance, Quality of interactions, Sleep). The somatic distress score peaked at study D7 then gradually improved in both arms (Figure S1).

For the daily inpatient activity scores (maximum score 5), median scores were higher, suggesting less fatigue, in the restrictive arm than in the liberal arm for both the parent and child (≥8 years old) scores, across the entire study period and during the first 35 days when the number of observations in both arms was the greatest (Figure S2). However, a similar difference between the two groups was seen at baseline, although the numbers were small.

Safety

Similar Serious Adverse Event (SAE) rates were reported (11 in the restrictive arm vs. 13 in the liberal), mostly admissions for febrile episodes.

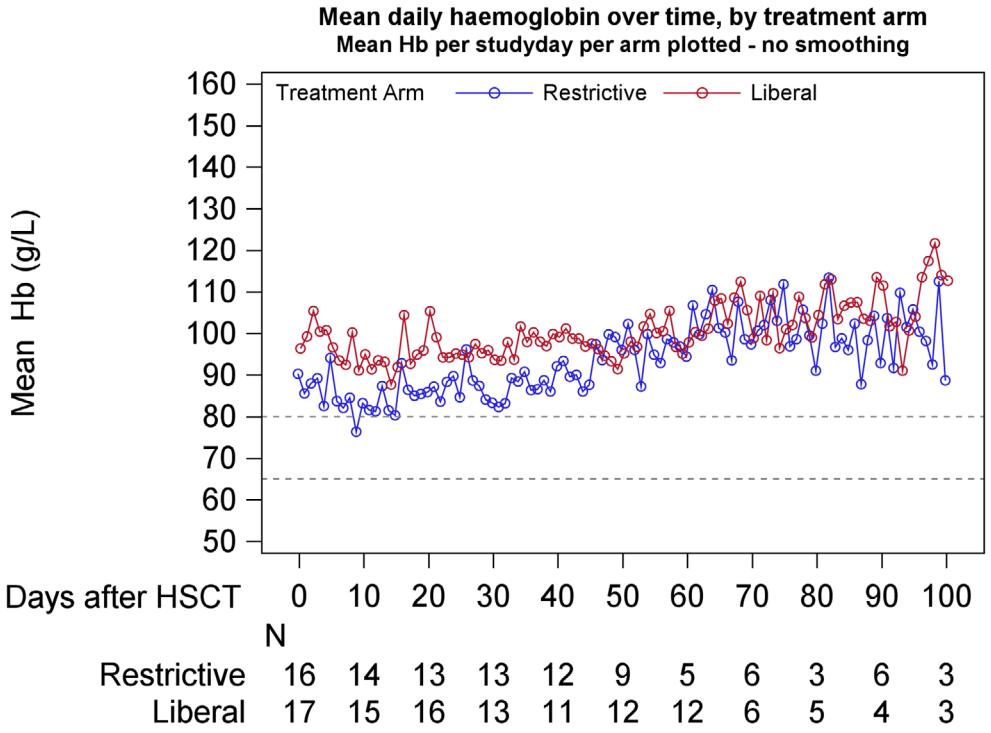

FIGURE 4 Mean daily haemoglobin over time, by trial arm. The figure includes available daily Hb measurements with the exception of observations post patient withdrawal. The *N*s in this figure are the number of observations on each of the specified days on the *x*-axis. Data in the graph are presented for all days between 0 and 100, but the *N* for every day could not be presented in the figure. The dotted lines represent the transfusion thresholds for the two arms.

DISCUSSION

Key findings from this feasibility trial of Hb thresholds in children undergoing HSCT were: (1) good measures of adherence above predefined targets (the percentage of Hb measurements where transfusions were given in accordance with the randomized policy) and a recruitment rate only just below target; (2) evidence of clinically significant separation between arms for Hb, with mean pre-transfusion Hb 16.3 g/L higher in the liberal arm; (3) no evidence to support that the use of a restrictive Hb arm of 65 g/L was associated with safety concerns or increased fatigue. The findings support the exploration of more restrictive thresholds for transfusion, below 70 g/L in children.

A number of learning points were identified by the conduct of this trial. Most Hb threshold-related protocol deviations were failure to transfuse when required. Adherence was stronger in the restrictive than liberal arm for Hb measurements at or below threshold, suggesting a reluctance in some cases to transfuse at the higher threshold. There were a small number of temporary protocol suspensions in the restrictive arm, for five participants. Overall, the number of transfusions per participant was the same in both arms, but this could have been impacted by weaker adherence to protocol in the liberal arm. Only the restrictive arm had non-transfused participants.

Despite the good separation in mean pre-transfusion Hb (16.3 g/L), the difference between study arms for overall Hb was only 7.5 g/L, and for post-transfusion Hb, 6.2 g/L. The smaller difference in post-transfusion Hb between arms might reflect the differential adherence to the study protocol for transfusion volume between the arms: despite equivalent Hb targets of 20 g/L above the Hb thresholds in both arms, the median transfusion volume (mL/kg) in the restrictive arm was higher than in the liberal. Where the volume given was incorrect according to protocol, there was a greater tendency to overtransfuse in the restrictive arm and to undertransfuse in the liberal. It is acknowledged that there is uncertainty about the optimum dose to transfuse; although the study protocol dose reflected current national guidelines,[2] it was more restrictive than much UK paediatric haematology/oncology practice.

Clinical secondary outcomes were broadly similar across arms. Three participants experienced significant bleeding, and there were more platelet transfusions per participant in the restrictive arm, but the clinical significance is uncertain given the small numbers. Bleeding is an important clinical outcome of restrictive transfusion studies, given that reduced numbers of circulating red cells may impair clot formation,[15] although supporting data are limited.[16] For aGvHD, the incidence, severity and duration of the highest grade were lower in the restrictive than in the liberal arm.

The impact of haemoglobin thresholds on measures of QoL is an area of active research interest, although most trial data are based in adults.[17] We applied the Behavioural, Affective, and Somatic Experiences Scale (BASES) tool, which has broad value in children receiving intensive therapy,[13,14] but, as for all tools, there may be questions about

validity to identify all relevant changes. In our study, the parent-reported somatic distress score peaked at the first week of the study, similar to previous reports using the BASES score in paediatric HSCT.[13,14] The daily activity inpatient score showed a trend to less fatigue in the restrictive arm, but there was a similar baseline difference.

Our study was not powered to assess the impact of haemoglobin thresholds on measures of QoL, and the numbers were small for the weekly assessed domains. While our study design focused primarily on the activity score, given it was considered the most likely to be directly affected by Hb levels, other domains such as somatic distress, mood disturbance and sleep may be equally important as outcomes in the setting of HSCT and warrant further exploration in a future study. Overall, there was no evidence of increased fatigue in the restrictive arm despite the lower Hb, and lower Hb thresholds were not associated with a negative impact on QoL. It should be added that a higher proportion of participants treated for AML were recruited in the restrictive arm (by chance), who might be expected to have more fatigue. Our findings appear consistent with other (adult) haematology/oncology studies,[17–21] although one study in chronically transfusion-dependent myelodysplastic syndrome suggested improved QoL in the liberal arm.[22]

There are a number of limitations to this feasibility study. It was small, not powered for clinical outcomes, including bleeding, and unblinded. Data completeness was less good for QoL, there was an activity score difference between arms at consent, and QoL data were only collected for inpatients (apart from consent and D100), when participants were least well. The study collected no data on longer term outcomes beyond D100.

Overall, our findings support the design of further studies addressing Hb thresholds below 70 g/L in children undergoing HSCT, which would minimize risks of exposure of children to transfusions, given these are biological products with risks. A future trial design should build on this feasibility study, powered for clinical outcomes and including outpatient QoL data with longer term follow-up. In addition, it should consider patient factors that may further influence an individual's tolerability of low Hb, as part of the future research interest towards personalized transfusion thresholds, rather than relying on Hb thresholds alone. Without any benefit for outcomes of reduced mortality or better QoL in the liberal arm, our findings are consistent with general recommendations to adopt restrictive transfusion practices in haematology cancers.

AUTHOR CONTRIBUTIONS

Study design: HVN, SJS, HT, AG, MA, LH, HS; data collection: AG, BG, CP, RW, LH; database: ML-C; statistics: ES, HT, LS; trial management: VH, HS, AM. All authors approved the manuscript.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the participants and families who agreed to take part, and all the hospital staff and research teams who helped to conduct the study. The study was supported by the NHSBT Clinical Trials Unit (CTU), including Alison Deary, Claire Rourke, Amy Evans, Renate Hodge, Katie Keen, Siobhan Martin, Lisha Gracias, Jo Bunnett, Dianne Bautista and Jenni Banks. We also thank Adrian Newland, Paul White, Gavin Murphy, Cheng-Hock Toh (Data and Safety Monitoring Committee) and Andrew Gennery, Georgina Hall and Lani Lieberman (Trial Steering Committee) and Kim Lacey for administrative support.

FUNDING INFORMATION

The study was funded by a grant from the NHS Blood and Transplant Trust Fund (TF070).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data requests should be submitted to the corresponding author or the NHSBT CTU for consideration. Access to anonymized data may be granted following review.

ETHICS STATEMENT

The study (ISRCTN17438123) was undertaken according to the Declaration of Helsinki and Good Clinical Practice principles. The protocol was approved by the Camden and Kings Cross Research Ethics Committee, London (Rec 19/LO/0714). The sponsor and funder had no role in the collection, analysis and interpretation of data, the writing of the publication or the decision to submit.

PATIENT CONSENT STATEMENT

Parental consent was carried out for all participants, according to UK Health Research Authority (HRA) guidance and good clinical practice guidelines.[23]

TRIAL PROTOCOL

The trial protocol is available upon request from the NHSBT CTU.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: New HV, Sanderson E, Hopkins V, Thomas H, Gassas A, Adams M, et al. How low can we go? Comparison of liberal and restrictive red cell transfusion thresholds in paediatric allogeneic haematopoietic stem cell transplantation: A randomized multicentre feasibility trial. Br J Haematol. 2025;00:1–11. https://doi.org/10.1111/bjh.20051