



SAHaRA

Aneurysmal SubArachnoid Hemorrhage – Red Blood Cell Transfusion And Outcome Trial:

Statistical Analytical Plan



NCT 03309579

Statistical Analysis Plan

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Revision Control

Protocol Version	Updated SAP version number	Section number changed	Description of change	Date changed
3.0	1.0			
3.0	1.1*	5.2	<p>12 month mortality to be presented as risk ratio rather than hazard ratio to harmonize approach with hospital mortality</p> <p>Error correction: tertiary outcome presented as proportion (AE) to be analyzed with GLMM rather than quantile regression</p> <p>Table 4 updated to reflect above</p>	Sept 13/24

*These adjustments do not constitute a change to the overall analytic plan, and were made prior to the database lock and opening of the randomization code.

SAP Signatures

SAP Version Number being approved: 1.1

I give my approval for the attached SAP entitled SAHaRA Trial dated September 13, 2024

Trial Statistician

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Signature: *Ranjeeta Mallick*

Date: September 13, 2024

Senior Statistician


Name: Tim Ramsay

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Roles and responsibilities

Name	Role	Institution
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Contributions

Shane English, Tim Ramsay, Peter Greenstreet and the SAHaRA Trial Executive Committee developed the statistical analysis plan (SAP) based on the outlined analyses set out in the trial protocol. Ranjeeta Mallick is the trial statistician and helped answer questions related to trial data and management relevant to the development of the SAP. The SAHaRA Trial Executive have reviewed and approved the SAP.

Abbreviations and Definitions

aSAH – aneurysmal subarachnoid hemorrhage

CBS – Canadian Blood Services

CIHR – Canadian Institutes of Health Research

CT - Computed Tomography

DCI – delayed cerebral ischemia

DSMB - Data Safety Monitoring Board

EQ-5D- 5L - EuroQOL Quality of Life Scale 5-Dimension 5-Level

eSAE - expected Serious Adverse Events

FIM - Functional Independence Measure

HAU - high-acuity unit

Hb - hemoglobin

MCID - minimal clinically important difference

mFS – modified Fisher Scale

mRS – modified Rankin Scale

RCT – randomized controlled trial

SAP – statistical analytic plan

uSAE -unexpected Serious Adverse Events

VAS – visual analogue scale

WFNS – World Federation of Neurological Surgeons

Section 1: Introduction

1.1 Background and Rationale

Aneurysmal subarachnoid hemorrhage (aSAH) is an important disease with devastating outcomes. Morbidity can be profound, with less than one third of survivors achieving a full functional recovery.¹ Anemia is common in these patients and is a potential critical factor affecting secondary injury, an often-protracted process.²⁻⁶ Despite physiologic evidence⁷ and management guidelines^{8,9} that support maintaining a higher hemoglobin level in patients with aSAH, stated current practice from surveys¹⁰ and from our multi-center cohort study¹¹ favors a more restrictive approach to transfusion in a similar fashion to other critical care patients^{12,13}. The clinical importance of varied transfusion thresholds in aSAH has never been studied in a large and rigorous randomized trial. In collaboration with the Canadian Critical Care Trials Group, we are conducting an open-label single blind RCT in adult patients with aSAH to examine the effect of a liberal compared to restrictive RBC transfusion strategy (Hb trigger $\leq 100\text{g/L}$ vs $\leq 80\text{g/L}$ respectively) on 12-month functional neurologic outcome.

1.2 Objectives

Our primary objective:

To evaluate the effect of a liberal (Hb trigger $\leq 100\text{g/L}$) versus a restrictive (Hb trigger $\leq 80\text{g/L}$) RBC transfusion strategy in acute aSAH patients with anemia ($\text{Hb} \leq 100\text{g/L}$) on patient-oriented functional neurologic outcome at 12 months.

Our secondary objectives:

To evaluate the effect of a liberal versus a restrictive RBC transfusion strategy on: a) 12-month overall function; b) quality of life at 12 months; c) mortality; d) delayed cerebral ischemia and radiographic vasospasm and e) clinically relevant stroke at hospital discharge on routine brain imaging.

Our tertiary objectives:

To evaluate the effect of a liberal versus a restrictive RBC transfusion strategy on lowest daily hemoglobin levels, RBC transfusions, expected and transfusion-related adverse events, mechanical ventilation and ICU and hospital length of stay.

Section 2: Study Methods

2.1 Trial Design

SAHaRA is a multicenter pragmatic randomized trial in patients with aSAH that compares the effect of a liberal to a restrictive RBC transfusion strategy on the combined rate of death and severe disability at 12 months. Our PROBE (prospective, open-label, blinded endpoint) approach has been informed by and tested in our CIHR/CBS-funded pilot RCT.¹⁴

Trial interventions

Eligible patients are randomized to either a restrictive or a liberal RBC transfusion strategy. Hemoglobin is checked at least daily while on protocol up to and including Day 10 post aSAH or while in an ICU/HAU (high-acuity unit), and then at the discretion of the primary clinical team.

Restrictive RBC Transfusion Strategy: For patients randomized to this group, an RBC transfusion is permitted once a hemoglobin level of ≤ 80 g/L is observed over the first 21 days following aSAH. RBC transfusion below the threshold is not mandatory, rather “usual care” prevails, with the decision and timing of transfusion left to the discretion of the treating team.

Liberal RBC Transfusion Strategy: An RBC transfusion is triggered by a hemoglobin level of ≤ 100 g/L over the first 21 days in hospital following aSAH. Transfusion in this arm is mandatory.

Both Groups: All RBC transfusion orders are single unit unless the patient has active blood loss associated with hemodynamic instability (see section 9.1 of the protocol – see Appendix). In stable non-bleeding patients, a second unit of RBCs is given if a measured post-transfusion hemoglobin level remains below the patient’s assigned threshold. Protocol adherence and violations are discussed in section 9.1 of the protocol (see Appendix).

Duration of the intervention

The allocated transfusion strategy is applied from the time of randomization to 21 days after the original bleed, death or hospital discharge, whichever comes first. The first 21 days following aSAH represent the period of greatest vulnerability to the direct consequences of aSAH, and the sequelae, including DCI, that follow.

2.2 Randomization

A web-based central computer-generated randomization, stratified by centre, was undertaken from the sponsoring centre. Upon meeting the randomization criteria, patients were randomized in a 1:1 manner to either restrictive or liberal RBC transfusion strategy groups, stratified by site. Variable random blocks of 4 and 6 was used. For patients randomized to the restrictive group, an RBC transfusion is permitted once a hemoglobin level of ≤ 80 g/L is observed over the first 21 days following aSAH. For patients randomized to the liberal group, an RBC transfusion is permitted once a hemoglobin level of ≤ 100 g/L is observed over the first 21 days in hospital following aSAH. The trial is an open-label blinded-endpoint randomized control trial. All outcomes are ascertained by an assessor (trained and qualified study personnel) blinded to the intervention and who has had no part in the management of the patients.

2.3 Sample Size

Based on our foundation work and previously published literature, we anticipate unfavourable neurologic outcome (mRS score of ≥ 4) at 12 months in 40% of the restrictive arm group.^{8,11,15,16} Previous studies involving SAH patient populations have supported a minimal clinically important difference (MCID) of a 25% relative improvement in poor neurologic outcome.¹⁷ Therefore, to demonstrate a 25% relative improvement in event rate (i.e., from 40% to 30%), a total sample size of 740 patients (test of independent proportions¹⁸) is necessary given 80% power, a type I error of 5% and a conservative 3% loss to follow-up factor.

2.4 Interim Statistical analyses and stopping guidance

One full interim, blinded analysis after the first 370 patients randomized was reviewed by the Data Safety Monitoring Board (DSMB) guided by a pre-specified charter. The data was then

tested for efficacy using the Haybittle-Peto criterion ($p < 0.001$).¹⁹ At this point there was not enough evidence to stop the trial for efficacy. Due to using the Haybittle-Peto criterion the final analysis will be conducted at $p < 0.05$. Regular (biannual) reports of patient recruitment, intervention fidelity and adverse event reporting were provided to and reviewed by the DSMB.

2.5 Timing of final analysis

The trial enrolment is complete. Participant follow up continues, with the last 12-month follow-up assessment completed by end of July 2024. The data will be cleaned, verified, and locked. The publication of this SAP will occur prior to the database lock. Final analysis will commence once the final lock has been confirmed by the principal investigator. Unblinding will only occur once the primary and secondary analyses are complete.

2.6 Timing of outcome assessment

Primary outcome:

- a) Modified Rankin Scale (mRS) score [12 months]

Secondary outcome:

- a) Functional Independence Measure (FIM) [12 months]
- b) EuroQOL Quality of Life Scale 5-Dimension 5-Level (EQ-5D-5L) and visual analogue scale (VAS) [12 months]
- c) Mortality [in-hospital]
- d) Delayed Cerebral Ischemia and Radiographic Vasospasm [over the first 21 days in hospital]
- e) New cerebral infarction [in-hospital]

Tertiary outcome:

- a) Lowest daily hemoglobin level [over the first 21 days in hospital]
- b) Proportion of patients who have an RBC Transfusion [over the first 21 days in hospital]
- c) Expected and transfusion-related adverse events [over the first 28 days in hospital]
- d) Need for and duration of mechanical ventilation [in-hospital]
- e) Length of stay [in-hospital]

Section 3: Statistical Principles

3.1 Confidence Intervals and P-values

The statistical uncertainty of all estimates will be expressed as two-sided 95% confidence intervals. Therefore, the analyses for an unfavorable neurologic outcome will be tested at a 0.05 level of significance. A p-value will only be reported for the primary outcome.

3.2 Adherence and protocol deviations

The study adherence is measured in 2 domains:

1) Adherence to allocated transfusion threshold: This occurred if an RBC transfusion is given only in response to the transfusion threshold being crossed with the last hemoglobin measure prior to transfusion being below the appropriate threshold. *Non-adherence* will be considered to have occurred if a) an RBC transfusion occurs before a transfusion threshold is crossed; or b) in the liberal arm, a transfusion is not given following a threshold crossing. Non-adherence will be

considered a *deviation* if: 1) the early transfusion occurs within 5 g/L above the allocated threshold (e.g., ≤ 105 g/L for the liberal arm or ≤ 85 g/L for the restrictive arm) or, 2) in the liberal arm, an RBC transfusion does not occur for a hemoglobin measure up to 5 g/L below the threshold (i.e.: a transfusion does not occur for a hemoglobin of 95-100 g/L). All other threshold event non-adherences will be considered a protocol violation. Details on non-adherence (date and hemoglobin level prior to transfusion) and reasons for non-adherence will be recorded. In the event of an active blood loss associated with hemodynamic instability, as defined by the treating team, standard resuscitation practices prevail (including blood product administration). Transfusion under this circumstance would not be a protocol violation. The allocated transfusion strategy will resume when hemodynamic stability is achieved and it is the opinion of the treating team that active bleeding has stopped. Transfusion outside of hemoglobin thresholds for symptomatic anemia (as assessed by the bedside team) will be recorded, but not considered a protocol violation.

2) Adherence to transfusion protocol (timely transfusion): We endeavor not to exceed 6 hours from transfusion threshold event to transfusion initiation, in keeping with revascularization time performance measures in stroke literature.^{20,21} Transfusion protocol adherence is thus defined as an RBC transfusion initiated within 6 hours of threshold crossing, or Randomization. *Non-adherence* will be considered to have occurred if there is a delay of more than six hours between transfusion threshold event and transfusion initiation. Transfusions occurring more than 6 hours but within 24 hours will be considered a deviation. A protocol violation is a transfusion initiated greater than 24 hours from the threshold event. We documented reasons for non-adherence in the study case report form.

We will assess adherence by evaluating the number of:

- All protocol violations (per patient).
 - All transfusion threshold violations (per patient).
 - All time to transfusion violations (per patient).

3.3 Analysis populations

Intention to Treat population: this population includes all aSAH patients randomized except those who were a post-randomization exclusion, withdrew consent, or were lost to follow up.

Per Protocol Population: this population is the intention to treat population except those who had a protocol violation (as defined in 3.2).

The primary analysis of all outcomes will be conducted on the Intention to Treat population. A secondary, sensitivity analysis, on the Per Protocol population will also be conducted and reported separately, accompanied by a description of the population characteristics, in the supplement.

Section 4 – Trial Population

4.1 Eligibility

Inclusion Criteria:

1. Age ≥ 18 years old at time of SAH

2. First ever episode of aneurysmal SAH
3. Diagnosis of aSAH as confirmed by treating physician (e.g., neurosurgeon or neuro-interventionalist) and supported by blood in subarachnoid space (e.g., cranial imaging or CSF positive for xanthochromia, surgical visualization) that is the result of a ruptured aneurysm (e.g., direct visualization, cranial imaging or catheter angiogram)
4. Hb \leq 100g/L within 10 days following aSAH (defined by first day of hospital presentation)

Exclusion Criteria:

1. Physician and or family decision to withdraw/withhold active medical care at time of enrolment.
2. Active bleeding with hemodynamic instability at time of enrolment.
3. Patients with contraindication or known objection to blood transfusions.
4. SAH due to mycotic aneurysm, infundibulum and vascular malformations.

4.2 Withdrawal/Follow-up

When a patient is lost to follow-up their 12-month mRS score will be missing, therefore, this patient cannot be included in the analysis of the primary outcome. Whenever possible, these patients will be included in the secondary outcome analyses.

No data will be analysed for patients who withdraw consent, but such patients will be listed in the CONSORT diagram.

4.3 Baseline Patient Characteristics

Baseline characteristics of randomized patients include (see Table 3): age; sex; ethnicity; comorbidities; history of intracranial bleed, ischemic stroke, cocaine use; smoking history; aneurysm and SAH characteristics/grade; status of aneurysm and securing technique, any prior RBC transfusion, presence of Delayed Cerebral Ischemia (DCI) or radiographic vasospasm (RV), presence of cerebral infarct (CI), and any cardiovascular vasopressor/inotropic therapy prior to randomization, and hemoglobin at randomization. Further characteristics may be included, and adjustments can be made to the report format to meet editorial guidelines.

Section 5 – Analysis

5.1 Outcome Definition

Primary outcome:

- Our primary outcome is the proportion of patients with unfavorable neurologic outcome (defined as mRS score of \geq 4 – see Table 1) at 12 months.

*Table 1: The Modified Rankin Scale**

<u>Score</u>	<u>Description</u>
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all ADLs
2	Slight disability; unable to carry out previous activities, but able to look after own affairs with assistance
3	Moderate disability; requiring some help but walks without assistance

4	Moderately severe disability; unable to walk unassisted and unable to look after own bodily needs unassisted
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

*modified from Washington University in St. Louis' Internet Stroke Center (www.strokecenter.org)

Secondary outcomes:

- Functional Independence Measure (FIM) at 12 months. The FIM is a validated tool consisting of 18 items that assesses 13 different motor and 5 cognitive tasks each measured on an 8-point scale (see Table 2). As we expect that death will not be affected by the intervention, deceased patients will be given the lowest score.²² It has demonstrated excellent consistency in inter-rater reliability and internal consistency specifically in neurologic disorder populations. It is easy to administer and is validated for use by telephone and via proxy respondents.

Table 2: the Functional Independence Measure**

I. Assessment Dimensions:		II. Scoring Criteria:		
1.	Eating	Score:	Description:	Category:
2.	Grooming	7	Complete independence	No Helper Required
3.	Bathing			
4.	Upper body dressing			
5.	Lower body dressing	6	Modified independence	No Helper Required
6.	Toileting			
7.	Bladder management	5	Supervision or setup	Helper - Modified Dependence
8.	Bowel management			
9.	Bed to chair transfer			
10.	Toilet transfer	4	Minimal contact assistance	Helper - Modified Dependence
11.	Shower transfer			
12.	Locomotion	3	Moderate assistance	Helper - Modified Dependence
13.	Stairs			
14.	Cognitive comprehension			
15.	Expression	2	Maximal assistance	Helper - Complete Dependence
16.	Social interaction			
17.	Problem solving			
18.	Memory	1	Total assistance	Helper - Complete Dependence
		0	Activity does not occur	

**modified from Rehabilitation Measures Database (www.rehabmeasures.org)

- EuroQOL Quality of Life Scale 5-Dimension 5-Level (EQ-5D- 5L) (generic scale) questionnaire is conducted at 12 months. It consists of a short and simple 5-part questionnaire and a visual analogue scale (VAS). It may be self-administered,

completed by interview or via a proxy respondent, and is used to value and describe health states. The questionnaire data is reported as an index value - a continuous fractional outcome with boundaries between zero and one. Zero represents the worst health status and 1 the best. The EQ-VAS (visual analogue scale) is a self-administered visual scale in which respondents rate from 0 to 100 (worst and best state of health respectively) their perceived health-related quality of life at the time of response. In analyses including non-survivors, deceased patients will be given the lowest score.²²

- Death in hospital.
- Delayed Cerebral Ischemia (DCI): defined as an otherwise unexplained decrease in Glasgow Coma Scale score of ≥ 2 points or new focal neurological deficit for ≥ 1 hour.
- Radiographic vasospasm: defined as a reduction of cerebral artery diameter on digital subtraction angiography (classified as mild [0-33% reduction], moderate [34-66% reduction] or severe [67-100% reduction]) or by transcranial Doppler of the middle or anterior cerebral artery (classified as mild [mean flow velocity of ≥ 120 and < 160 cm/sec AND Lindegaard ratio ≥ 3], moderate [mean flow velocity of ≥ 160 and < 200 cm/sec AND Lindegaard ratio ≥ 3] or severe [mean flow velocity of ≥ 200 cm/sec AND Lindegaard ratio ≥ 3]). This is considered incident if it occurs after randomization.
- New Cerebral infarction: defined a new area of infarcted brain (not present) at time of randomization, as captured on routine cranial imaging (e.g., CT or MRI) during the initial hospitalization. It is characterized as related to DCI/vasospasm, to complications from securing the ruptured aneurysm or other/unknown.

Tertiary Outcomes:

- Lowest daily hemoglobin level over the first 21 days in hospital
- Proportion of patients receiving at least one RBC transfusion
- Median number of RBC units transfused
- Expected adverse events of the first 28 days in hospital
- Transfusion-related adverse events of the first 28 days in hospital
- need for and duration of invasive mechanical ventilation – defined as mechanical ventilation delivered via either endotracheal intubation or tracheostomy
- ICU length of stay
- Hospital length of stay

5.2 Analysis Methods

Unless otherwise specified, all analyses will be completed on the intention to treat population (see section 3.3). Given the pragmatic nature of the trial, and possible variations in practice from centre to centre, randomization was stratified by centre. As such, all primary analyses are adjusted for centre and sex as aSAH predominantly affects females. In summary, unless stated otherwise below, all parametric analyses will be conducted using Generalized Linear Mixed Models (GLMM) with fixed effects for treatment and sex, and a random effect for centre. Non parametric median estimates will be conducted using quantile regressions adjusting for site and sex. A summary of the proposed analyses is presented in Table 4.

Primary Outcome:

Primary analysis:

- The main statistical analysis will be done on the intention to treat population with a binomial GLMM with log-link function and reported as a risk ratio with corresponding 95% confidence interval.

Secondary analysis:

- For the primary outcome a proportional odds analysis, will additionally be conducted. The proportional odds assumption will be tested using the Brant-Wald test at the alpha level of 5%.

Sensitivity analysis:

Sensitivity analysis of the primary outcome will be tested in 4 ways:

- Further adjusted with WFNS and age as additional fixed effects
- We chose dichotomized mRS scores as the results of the analysis are simple to understand and interpret, but the cut-off is arbitrarily chosen and information is lost by dichotomization. Therefore, we will repeat the primary analysis with unfavorable neurologic outcome defined as mRS ≥ 3 rather than ≥ 4 .
- Per protocol analysis (see section 3.3)
- Best case-worst case scenario. In this sensitivity analysis of the primary outcome, we will include randomized patients in which the primary outcome is missing – e.g. withdrawal or lost to follow-up. Patients who were randomized in error will be excluded. Two scenarios will be considered:
 - Best-case scenario: a favourable outcome will be imputed for those in the liberal transfusion strategy arm with missing primary outcome, and unfavourable outcome to those in the restrictive transfusion strategy arm with missing primary outcome.
 - Worst-case scenario: an unfavourable outcome will be imputed for those in the liberal transfusion strategy arm with missing primary outcome, and a favourable outcome to those in the restrictive transfusion strategy arm with missing primary outcome.

Secondary Outcomes:

- The Functional Independence Measure as well as Motor and Cognition sub-scores will be analysed using a linear GLMM with an identity link function. The treatment effect will be reported as a mean difference with 95% CIs. In addition, the same analyses will be done however now excluding patients who are deceased.
- EQ-5D-5L Visual Analogue Scale will be analysed using a linear GLMM with an identity link function. The treatment effect will be report as a mean difference with 95% CIs. In addition, the same analyses will be done however now excluding patients who are deceased.
- Mortality in hospital will be analysed using a log-binomial GLMM and reported as a risk ratio with 95% CI.
- Mortality at 12 months will be analysed using a log-binomial GLMM and reported as a risk ratio with 95% CI.
- The number of patients with new cerebral infarction, DCI, and radiographic vasospasm, post randomization will be analysed using a log-binomial GLMM and reported as a risk ratio with 95% CI.

Tertiary Outcomes:

- Lowest daily hemoglobin level over the first 21 days in hospital will be presented graphically as means with 95% confidence intervals per group

- Proportion of patients receiving RBC transfusion with between group differences analysed using using a log-binomial GLMM
- Median number of RBC units transfused will be reported with interquartile ranges and presented as median difference with 95% CI using quantile regression analyses adjusting for site and sex.
- Proportion of patients with expected and transfusion-related adverse events will be reported with between group differences analysed using using a log-binomial GLMM adjusting for site and sex
- Duration of invasive mechanical ventilation will be reported as presented as median difference with 95% CI using quantile regression analyses adjusting for site and sex.
- ICU and Hospital Length of stay will also be described as medians with interquartile ranges and presented as median differences with 95% CI using quantile regression analyses adjusting for site and sex.

Pre-planned Subgroup Analyses:

We plan exploratory subgroup analyses for the primary outcome (as described above) in the following groups:

- Age: ≤ 55 years versus >55 years-old. We hypothesize that a liberal transfusion strategy is more effective in those over the age of 55. SAH incidence increases with age, especially those >55 years (mean age), and increased age is associated with worse outcome.²³ Previous transfusion trigger trials have demonstrated less benefit of a liberal transfusion trigger in those less than age 55.¹³ This subgroup has been explored in other large SAH²⁴ and transfusion trigger trials¹³.
- Sex: female sex versus male sex. We hypothesize no treatment effect difference between male and female sex.
- Clinical condition at admission: using the World Federation of Neurological Surgeons Score. We hypothesize that a liberal transfusion strategy is more effective in those with worse clinical condition at presentation. Worse clinical grade at presentation is associated with anemia and unfavourable outcome.^{6,23}
- Radiographic grade at admission: using the modified Fisher Scale. We hypothesize that a liberal transfusion strategy is more effective in those with higher grades. Worse radiographic grade at presentation is associated with anemia and unfavourable outcome.^{6,11,23}
- Method of treatment of Aneurysm: neurosurgical (craniotomy) extravascular versus endovascular aneurysm intervention. We hypothesis that a liberal transfusion strategy is more effective in those with extravascular interventions. Neurosurgical (craniotomy) management of ruptured aneurysms is associated with worse anemia and has greater morbidity.^{11,17}
- Baseline DCI: present at randomization vs not. We hypothesize that a liberal transfusion strategy is more effective in those with DCI at baseline. DCI is associated with anemia⁶. Transfusion in anemic patients with DCI is associated with less ischemic burden.²⁵⁻²⁸
- Baseline Radiographic Vasospasm: present at randomization vs not. We hypothesize that a liberal transfusion strategy is more effective in those with vasospasm at baseline. Vasospasm is associated with anemia⁶. Transfusion in anemic patients with vasospasm is associated with less ischemic burden.²⁵⁻²⁸

5.3 Missing Data

First, every attempt will be made to retrieve the missing data. All missing data will be reported and the frequencies of these will be calculated. We will not impute data for missing outcomes.

For all adjusted analyses, we will use multiple imputation to impute missing covariates, assuming that the *missing completely at random* or *missing at random* assumptions are plausible. We will use MICE using the MI and MIANALYZE procedures in SAS (version 9.4) with the number of imputations corresponding to the fraction of missing data.²⁹

5.4 Harms

Adverse Event Reporting

- Expected Serious Adverse Events (eSAE). These events have been defined a priori and are being collected and reported as study outcomes and as such will not be labelled nor reported a second time as serious adverse events.
- Unexpected Serious Adverse Events (uSAE). All uSAEs are to be brought to the attention of the site PI (following site specific standard operating procedures). Causality (see section 7.3.4 of protocol) of the uSAE should be adjudicated by the site PI. All possibly or related uSAEs are to be reported in the Data Collection Forms (both study arms) as described in this section:
 - Monitoring and reporting should begin on the first day of study intervention and continue until either:
 - the uSAE has been resolved
 - day 28 (post-ictal bleed), death or discharge whichever occurs first
 - if the uSAE remains ongoing at day 28 it will be reported as such
 - Supporting source documentation of all reported uSAEs must be submitted for additional and final central adjudication.
 - Abnormal laboratory results do not need to be recorded unless considered by the investigator to be relevant in terms of subject or trial safety (or in relation to a serious adverse event that is being reported).
- Serious Adverse Event Reporting. All reportable unexpected SAEs must be reported to the Coordinating Centre within 72 hours of the site's knowledge of the unexpected SAE. The Study Chair and/or Study Steering Committee will review all unexpected SAE's received from the sites. If an unexpected SAE is confirmed, a document summarizing the SAE will be distributed to participating sites. Sites should follow the guidelines of their local REB with respect to the submission of SAEs that occur at the site as well as SAE Notifications.
- All reportable unexpected SAEs will be described with the presentation of the main results

Table 3: Baseline Characteristics

	Liberal Strategy (N=)	Restrictive Strategy (N=)
<u>PATIENT DEMOGRAPHICS</u>		
Age, years		
	Mean (SD)	
	Median (IQR)	
Sex		
	Female (%)	
	Male (%)	
Race or ethnicity (%)		
	Asian	
	Black	
	First Nations	
	Hispanic	
	White	
	other	
Relevant medical history (%)		
	Hypertension	
	Current or previous smoker	
	Ischemic heart disease	
	Congestive heart failure	
	History of ICH	
	Ischemic stroke	
	End-stage renal disease	
	Chronic anemia	
Time from first hospital presentation to randomization, days		
	Mean (SD)	
	Median (IQR)	
Country of Randomization (%)		
	Canada	
	USA	
	Australia	
<u>SAH CHARACTERISTICS</u>		
Admission WFNS, (%)⁺		
	5	
	4	
	3	
	2	
	1	
	Median (IQR)	
modified Fisher Grade (%)[‡]		
	4	
	3	
	2	
	1	
	Median (IQR)	
Aneurysm Location (%)		
	Anterior circulation	
	Posterior circulation	
Aneurysm Treatment (%)		
	Coiling/Endovascular	
	Clipping	
	No Treatment	
EVD (%)		
Presence of DCI or RV (%)		
	DCI	

	RV
Presence of Cerebral infarction (%)	
Cardiovascular vasopressor/inotropic therapy (%)	
Prior RBC Transfusion, (%)	
Hemoglobin at randomization, g/dL	
	Mean (SD)
	Median (IQR)

+ World Federation of Neurological Surgeons: 1=GCS 15, 2=GCS 13-14 and no focal deficit, 3=GCS 13-14 AND focal deficit, 4=GCS 7-12, 5=GCS <7

¥ modified Fisher Grade: 0: no SAH no IVH, 1: thin diffuse or focal SAH and NO IVH; 2: thin diffuse or focal SAH with IVH; 3: thick focal (>1mm) or diffuse SAH and NO IVH; 4: thick focal (>1mm) or diffuse SAH with IVH

DCI=delayed cerebral ischemia, EVD=externalized ventricular drain, GCS=Glasgow Coma Scale, IQR=interquartile range, RV=radiographic vasospasm, SAH=subarachnoid hemorrhage, SD=standard deviation, WFNS=World Federation of Neurological Surgeons

Table 4: Statistical Analytical Plan Summary

	Main Analysis*	Sensitivity analyses for the main analysis	Additional analyses	Adjustments**
Primary Outcome:				
mRS at 12 months	<ul style="list-style-type: none"> Log-binomial GLMM with fixed effects for treatment and sex, and a random effect for centre, reported as a risk ratio with 95% CI 	<ul style="list-style-type: none"> Further adjusted with WFNS and age as fixed effects Unfavorable neurologic outcome defined as mRS ≥ 3 rather than ≥ 4 Per protocol analysis[†] Best case – worst case scenarios[‡] 	<ul style="list-style-type: none"> Proportional odds analysis using the Brant-Wald test 	<ul style="list-style-type: none"> Centre Sex
Secondary Outcomes:				
FIM	<ul style="list-style-type: none"> Linear GLMM and reported as mean difference with 95% CI 	<ul style="list-style-type: none"> Excluding deceased patients 	<ul style="list-style-type: none"> Unadjusted model 	<ul style="list-style-type: none"> Centre Sex
EQ-5D-5L VAS	<ul style="list-style-type: none"> Linear GLMM and reported as mean difference with 95% CI 	<ul style="list-style-type: none"> Excluding deceased patients 	<ul style="list-style-type: none"> Unadjusted model 	<ul style="list-style-type: none"> Centre Sex
Mortality – hospital	<ul style="list-style-type: none"> log-binomial GLMM and reported as a risk ratio with 95% CI 	-	<ul style="list-style-type: none"> Unadjusted model 	<ul style="list-style-type: none"> Centre Sex
Mortality – 12 months	<ul style="list-style-type: none"> log-binomial GLMM and reported as a risk ratio with 95% CI 	-	<ul style="list-style-type: none"> Unadjusted model 	<ul style="list-style-type: none"> Centre Sex
New cerebral infarction	<ul style="list-style-type: none"> log-binomial GLMM and reported as a risk ratio with 95% CI 	-	<ul style="list-style-type: none"> Unadjusted model 	<ul style="list-style-type: none"> Centre Sex
New DCI	<ul style="list-style-type: none"> log-binomial GLMM and reported as a risk ratio with 95% CI 	-	<ul style="list-style-type: none"> Unadjusted model 	<ul style="list-style-type: none"> Centre Sex
New radiographic vasospasm	<ul style="list-style-type: none"> log-binomial GLMM and reported as a risk ratio with 95% CI 	-	<ul style="list-style-type: none"> Unadjusted model 	<ul style="list-style-type: none"> Centre Sex
Tertiary Outcomes:				
Lowest daily hemoglobin	<ul style="list-style-type: none"> Presented graphically with 95% CI, per group 	-	-	-
Proportion of patients, per group, receiving RBC transfusion	<ul style="list-style-type: none"> Log-binomial GLMM 	-	<ul style="list-style-type: none"> Unadjusted model 	<ul style="list-style-type: none"> Centre Sex
Number of RBC units transfused	<ul style="list-style-type: none"> Presented as median difference with 95% CI using quantile regression 	-	<ul style="list-style-type: none"> Median with IQR 	<ul style="list-style-type: none"> Centre Sex

Expected and transfusion-related adverse events	<ul style="list-style-type: none"> • Log-binomial GLMM 	-	<ul style="list-style-type: none"> • Median with IQR 	<ul style="list-style-type: none"> • Centre • Sex
Duration of mechanical ventilation	<ul style="list-style-type: none"> • Presented as median difference with 95% CI using quantile regression 	-	<ul style="list-style-type: none"> • Median with IQR 	<ul style="list-style-type: none"> • Centre • Sex
Length of stay in the ICU and hospital	<ul style="list-style-type: none"> • Presented as median difference with 95% CI using quantile regression 	-	<ul style="list-style-type: none"> • Median with IQR 	<ul style="list-style-type: none"> • Centre • Sex

* Unless otherwise stated, all analyses will be conducted on the Intention to treat population: includes all aSAH patients randomized except those who were a post-randomization exclusion, withdrew consent, or were lost to follow up.

** Adjustments for all listed analyses unless otherwise specified

† Per-protocol population includes the intention to treat population (all aSAH patients randomized except those who were a post-randomization exclusion, withdrew consent, or were lost to follow up), but excludes those who had a protocol violation.

‡ In the best-case scenario: a favourable outcome will be imputed for those in the liberal transfusion strategy arm with missing primary outcome, and unfavourable outcome to those in the restrictive transfusion strategy arm with missing primary outcome. In the worst-case scenario: an unfavourable outcome will be imputed for those in the liberal transfusion strategy arm with missing primary outcome, and a favourable outcome to those in the restrictive transfusion strategy arm with missing primary outcome.

CI – confidence interval; DCI – delayed cerebral ischemia; EQ-5D-5L VAS – EuroQOL 5 dimensions 5 levels Visual Analogue Scale; FIM – Functional Independence Measure; GLMM – Generalized linear mixed methods; ICU – Intensive Care Unit; IQR – Interquartile Range; mRS – modified Rankin Scale; RBC – Red blood cell; WFNS – World Federation of Neurological Surgeon

Section 6 – References

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