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

Statistical Analytical Plan

NCT 03309579

Statistical Analysis Plan

Date	**2024 June 14**
SAP Version Number	*Version 1.0 14/06/2024*
Protocol Version and Date	*Version 3.0 (03/09/2020)*
Senior Statistician (Blinded)	*Tim Ramsay*
Trial Statistician	*Ranjeeta Mallick*
Data Manager - Programmer	*Anton Saarimaki*
Trial Chief Investigator	*Shane English*
SAP Authors	*Shane English* *Tim Ramsay* *Anthony Delaney* *Alexis Turgeon* *Lauralyn McIntyre* *Dean Fergusson* *François Lauzier* *Michaël Chassé* *Don Griesdale* *Alan Tinmouth* *Irene Watpool* *Peter Greenstreet*

Revision Control

Protocol Version	Updated SAP version number	Section number changed	Description of change	Date changed

SAP Signatures

SAP Version Number being approved: 1.0

I give my approval for the attached SAP entitled SAHaRA Trial dated June 14, 2024

Trial Statistician

Name: Ranjeeta Mallick

Signature: ranjeeta mallick

Date: July 18, 2024

Senior Statistician

Name: Tim Ramsay

Signature: Tim Ramsay

Date: July 17, 2024

Chief Investigator

Name: Shane English

Signature:

Date: July 17, 2024

Roles and responsibilities

Name	Role	Institution
Ranjeeta Mallick	*Trial Statistician*	*OHRI - Ottawa Methods Centre*
Shane English	*Chief Trial Investigator*	*University of Ottawa*
Tim Ramsay	*Senior Statistician (Blinded)*	*OHRI - Ottawa Methods Centre*

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 evidence[7] and management guidelines[8,9] that support maintaining a higher hemoglobin level in patients with aSAH, stated current practice from surveys[10] and from our multi-center cohort study[11] 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 ≤100g/L vs ≤80g/L respectively) on 12-month functional neurologic outcome.

1.2 Objectives

Our primary objective:

To evaluate the effect of a liberal (Hb trigger ≤100g/L) versus a restrictive (Hb trigger ≤80g/L) RBC transfusion strategy in acute aSAH patients with anemia (Hb≤100g/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 ≤80g/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 ≤100g/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 ≤80g/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 ≤100g/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 proportions[18]) 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 ≤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 ≥4 – see Table 1) at 12 months.

*Table 1: The Modified Rankin Scale**

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

**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 summarized with Kaplan-Meier curves and Cox regression hazard ratios.
- 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 and presented as median difference with 95% CI using quantile regression analyses 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 SAH [24] and transfusion trigger trials[13].
- 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 anemia[6]. 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 anemia[6]. 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=)
PATIENT DEMOGRAPHICS		
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		
SAH CHARACTERISTICS		
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	• Log-binomial GLMM with fixed effects for treatment and sex, and a random effect for centre, reported as a risk ratio with 95% CI	• 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‡	• Proportional odds analysis using the Brant-Wald test	• Centre • Sex
Secondary Outcomes:				
FIM	• Linear GLMM and reported as mean difference with 95% CI	• Excluding deceased patients	• Unadjusted model	• Centre • Sex
EQ-5D-5L VAS	• Linear GLMM and reported as mean difference with 95% CI	• Excluding deceased patients	• Unadjusted model	• Centre • Sex
Mortality – hospital	• log-binomial GLMM and reported as a risk ratio with 95% CI	-	• Unadjusted model	• Centre • Sex
Mortality – 12 months	• Kaplan-Meier curves and Cox regression hazard ratios	-	• Unadjusted model	• Centre • Sex
New cerebral infarction	• log-binomial GLMM and reported as a risk ratio with 95% CI	-	• Unadjusted model	• Centre • Sex
New DCI	• log-binomial GLMM and reported as a risk ratio with 95% CI	-	• Unadjusted model	• Centre • Sex
New radiographic vasospasm	• log-binomial GLMM and reported as a risk ratio with 95% CI	-	• Unadjusted model	• Centre • Sex
Tertiary Outcomes:				
Lowest daily hemoglobin	• Presented graphically with 95% CI, per group	-	-	-
Proportion of patients, per group, receiving RBC transfusion	• Log-binomial GLMM	-	• Unadjusted model	• Centre • Sex
Number of RBC units transfused	• Presented as median difference with 95% CI using quantile regression	-	• Median with IQR	• Centre • Sex

Expected and transfusion-related adverse events	• Presented as median difference with 95% CI using quantile regression	-	• Median with IQR	• Centre • Sex
Duration of mechanical ventilation	• Presented as median difference with 95% CI using quantile regression	-	• Median with IQR	• Centre • Sex
Length of stay in the ICU and hospital	• Presented as median difference with 95% CI using quantile regression	-	• Median with IQR	• 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.

ǂ 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

1. Nieuwkamp DJ, Setz LE, Algra A, Linn FHH, de Rooij NK, Rinkel GJE. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet neurology [online serial]. Elsevier Ltd; 2009;8:635–642.
2. Naidech AM, Jovanovic B, Wartenberg KE, et al. Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. Crit Care Med. 2007;35:2383–2389.
3. Naidech AM, Drescher J, Ault ML, Shaibani A, Batjer HH, Alberts MJ. Higher hemoglobin is associated with less cerebral infarction, poor outcome, and death after subarachnoid hemorrhage. Neurosurgery. 2006;59:775–779.
4. Wartenberg KE, Mayer SA. Medical complications after subarachnoid hemorrhage. Neurosurg Clin N Am. United States: Department of Neurology, Neurologic Intensive Care Unit, Martin-Luther University, Halle-Wittenberg, Leipzig, Germany.; 2010;21:325–338.
5. Kramer AH, Gurka MJ, Nathan B, Dumont AS, Kassell NF, Bleck TP. Complications associated with anemia and blood transfusion in patients with aneurysmal subarachnoid hemorrhage. Crit Care Med. 2008;36:2070–2075.
6. Sampson TR, Dhar R, Diringer MN. Factors associated with the development of anemia after subarachnoid hemorrhage. Neurocrit Care . Department of Neurology, Washington University School of Medicine, 660 S. Euclid Ave, Campus Box 8111, Saint Louis, MO 63110, USA.; 2010;12:4–9.
7. Le Roux PD. Anemia and transfusion after subarachnoid hemorrhage. Neurocrit Care. 2011;15:342–353..
8. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke; a journal of cerebral circulation. 2012;43:1711–1737.
9. Diringer MN, Bleck TP, Claude Hemphill J, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. Humana Press Inc.; 2011;15:211–240.
10. Kramer A, Diringer M, Naidech A, Macdonald L, LeRoux P. Hemoglobin thresholds for a clinical trial comparing liberal and restrictive transfusion strategies in patients with aneurysmal subarachnoid hemorrhage: A multidisciplinary north american survey. Neurocrit Care A. Kramer, University of Calgary, Calgary, AB, Canada: Humana Press; 2010. p. S207.
11. English SW, Chasse M, Turgeon A, et al. Aneurysmal subarachnoid hemorrhage and anemia: a canadian multi-centre retrospective cohort study. Crit Care. 2016;20:P337.
12. Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med. 2007;356:1609–1619.

13. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340:409–417.

14. English SW, Fergusson D, Chassé M, et al. Aneurysmal SubArachnoid Hemorrhage—Red Blood Cell Transfusion And Outcome (SAHaRA): a pilot randomised controlled trial protocol. BMJ Open [online serial]. 2016;6:e012623.

15. Bederson JB, Connolly ES, Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke; a journal of cerebral circulation. Acm; 2009;40:994–1025.

16. Van Den Bergh WM, Algra A, Van Kooten F, et al. Magnesium sulfate in aneurysmal subarachnoid hemorrhage: a randomized controlled trial. Stroke: A Journal of Cerebral Circulation. Am Heart Assoc; 2005;36:1011–1015.

17. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet [online serial]. Elsevier Ltd; 2002;360:1267–1274.

18. Fleiss JL, Tytun A., Ury HK. A Simple Approximation for Calculating Sample Sizes for Comparing Independent Proportions. Biometrics. 1980;36:343–346.

19. Pocock SJ. When (Not) to Stop a Clinical Trial for Benefit. JAMA. 2005;294:2228.

20. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; a journal of cerebral circulation [online serial]. 2013;44:870–947.

21. Lindsay M, Gubitz G, Bayley M, et al. Canadian Best Practice Recommendations for Stroke Care (Update 2010). Ottawa ON Canada; 2010.

22. Colantuoni E, Scharfstein DO, Wang C, et al. Statistical methods to compare functional outcomes in randomized controlled trials with high mortality. BMJ [online serial]. Epub 2018 Jan 3.:j5748.

23. Hoh BL, Ko NU, Amin-Hanjani S, et al. 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke. Wolters Kluwer Health; 2023;54:E314–E370.

24. Dorhout Mees SM, Algra A, Vandertop WP, et al. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. Lancet. 2012;380:44–49.

25. Dhar R, Zazulia A, Videen T, Zipfel G, Diringer M. Transfusion may be more effective at improving cerebral oxygen delivery after subarachnoid hemorrhage at lower hemoglobin levels. Neurocrit Care. R. Dhar, Washington University, School of Medicine, Saint Louis, MO, United States: Humana Press; 2010;13:S12.

26. Dhar R, Zazulia AR, Videen TO, Zipfel GP, Diringer MN. Red blood cell transfusion may be more effective in augmenting cerebral oxygen delivery after subarachnoid hemorrhage at lower hemoglobin levels. Stroke; a journal of cerebral circulation; 2010. p. e327.

27. Dhar R, Scalfani MT, Zazulia AR, Videen TO, Derdeyn CP, Diringer MN. Comparison of induced hypertension, fluid bolus, and blood transfusion to augment cerebral oxygen delivery after subarachnoid hemorrhage. J Neurosurg. 2012;116:648–656.

28. Dhar R, Zazulia AR, Videen TO, Zipfel GJ, Derdeyn CP, Diringer MN. Red blood cell transfusion increases cerebral oxygen delivery in anemic patients with subarachnoid hemorrhage. Stroke. 2009;40:3039–3044.

29. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30:377–399.