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Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome (SAHaRA): A Pilot Randomized Controlled Trial Protocol

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1. ABSTRACT

Introduction: Anemia is common in aneurysmal subarachnoid hemorrhage (aSAH) and is a potential critical modifiable factor affecting secondary injury. Despite physiologic evidence and management guidelines that support maintaining a higher hemoglobin level in patients with aSAH, current practice is one of a more restrictive approach to transfusion. The goal of this multicenter pilot trial is to determine the feasibility of successfully conducting an RBC transfusion trial in adult patients with acute aSAH and anemia (Hb≤100g/L), comparing a liberal transfusion strategy (Hb≤100g/L) to a restrictive strategy (Hb≤80g/L) on the combined rate of death and severe disability at 12 months.

Methods: Design: This is a multi-center open-label randomized controlled pilot trial at five academic tertiary care centers. **Population:** We are targeting adult aSAH patients within 14 days of their initial bleed and with anemia (Hb ≤110g/L). **Randomization:** Central computer-generated randomization, stratified by center, will be undertaken from the host center. Randomization into one of the two treatment arms will occur when the hemoglobin levels of eligible patients fall to ≤100g/L. **Intervention:** Patients will be randomly assigned to either a liberal (threshold: Hb≤100g/L) or a restrictive transfusion strategy (threshold: Hb≤80g/L). **Outcome:** Primary: Center randomization rate over the study period. Secondary: a) transfusion threshold adherence; b) study RBC transfusion protocol adherence; and c) outcome assessment including vital status at hospital discharge, modified Rankin Score at 6 and 12 months and functional independence measure and EuroQOL Quality of Life Scale scores at 12 months. Outcome measures will be reported in aggregate.

Ethics and Dissemination: The study protocol has been approved by the host center (OHSN-REB 20150433-01H). This study will determine the feasibility of conducting the large pragmatic

RCT comparing 2 RBC transfusion strategies examining the effect of a liberal strategy on 12-month outcome following aSAH. (Trial Registry No.: NCT 02483351)

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating illness caused by the spontaneous rupture of a weakened and enlarged artery in the brain. It affects a young population and is a significant cause of premature death and loss of potential life years, at a similar magnitude of ischemic stroke.[1] It is a common neurologic reason for intensive care unit (ICU) admission[2] and is associated with a mortality rate of about 35% in North America (range 20-70%).[3] Less than one third afflicted make a full recovery[4] and 20% of survivors experience significant morbidity[5] having an impact on daily living.

Anemia (hemoglobin [Hb] <100g/L) affects more than 50% of aSAH patients and is associated with worse clinical outcomes.[4,6–11] Preclinical studies in brain injury suggest that red blood cell (RBC) transfusion to treat anemia optimizes oxygen delivery in this specific setting.[4] However, RBC transfusions are not without risk and are a limited and expensive resource.[12] The limited evidence examining the association between RBC transfusion and clinical outcome from aSAH is derived from few observational studies with conflicting results and significant methodological limitations.[5,7,9,10,13–17] Only one small trial compared two transfusion targets in aSAH but was underpowered to examine clinically important outcomes.[18] Despite this absence of evidence, current aSAH management guidelines include a recommendation to *consider* RBC transfusion in anemic patients *at risk* for cerebral ischemia, but do not suggest transfusion thresholds to guide clinicians.[19,20] These recommendations are in contrast with evidence from randomized controlled trials (RCTs) in other critically ill adult and pediatric populations which support a more restrictive RBC transfusion approach.[21,22]

Although both the biological rationale and current recommendations for treating aSAH patients support a higher transfusion threshold (liberal strategy), the clinical evidence is lacking

to substantiate these recommendations. Current stated and observed practice from surveys[23] and our own observational work suggest a more restrictive approach to transfusion (lower hemoglobin); similar to other critical care patients. However, unlike other critically ill patients, brain injury and the sequelae that follow (e.g.: vasospasm and delayed cerebral ischemia) may make these patients more susceptible to the decreased oxygen delivery associated with a lower transfusion threshold. Considering this obvious paradox and confliction, there is pressing need to generate high-quality evidence to guide clinical RBC transfusion practices in aSAH. The clinical impact 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 (www.ccctg.ca), we aim to conduct such an RCT comparing two RBC transfusion strategies in adult patients with aSAH powered for clinically relevant outcomes. To inform and justify our large trial, we are conducting a pilot RCT to assess feasibility and strengthen the design of the large-scale trial.

METHODS AND ANALYSIS

Study Design

The Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome: A Pilot Randomized Controlled Trial (SAHaRA Pilot Trial) is a Canadian multicenter (5) open-label randomized controlled pilot trial in patients with an acute aSAH. To reduce bias from the open-label design, outcome assessors will be blinded to the treatment assignments.

Patient Population

To facilitate randomization into the pilot trial, a subset of patients most likely to meet randomization criteria will be identified (Screen Eligible Patients). To be screened eligible for enrolment, patients must meet all inclusion criteria and no exclusion criteria.

Inclusion Criteria:

1. Age ≥18 years old at time of presentation
2. First ever episode aSAH
3. Confirmed aSAH diagnosis: as confirmed by treating neurosurgeon or neuro-interventionalist and supported by blood in subarachnoid space (demonstrated on cranial imaging or cerebrospinal fluid positive for xanthochromia) that is the result of a ruptured saccular aneurysm (confirmed by cranial imaging – computed tomography, magnetic resonance or catheter angiogram)
4. Incident Hb ≤110g/L within 14 days following aSAH (defined by first day of hospital presentation)

Exclusion Criteria:

1. Physician and or next of kin decision to withdraw/withhold critical 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 causes other than saccular aneurysm rupture including mycotic, traumatic and dissecting aneurysms, and aneurysms associated with arteriovenous malformations

Our exclusion criteria are in place to prevent enrolling patients who: 1) would not benefit from the intervention; 2) object to the intervention; and/or 3) have sustained a bleed due to mechanistically different causes whose pathophysiological properties are not necessarily shared with aSAH.

Screen eligible patients who experience an incident Hb ≤100 g/L within 14 days following aSAH will be randomized.

Randomization and Allocation Concealment:

Figure 1 provides a schematic description of the trial design. Local research coordinators will screen each patient admitted to either the intensive care unit, intermediate care unit or step-down unit (where applicable) or neurosurgical inpatient unit in the setting of aSAH for up to 14 days after the qualifying bleed. Enrolment and randomization over 14 days is necessary as previous work has demonstrated that the negative effect on outcome was most pronounced in patients with anemia between days 6 and 11.[24] Further, our observational study demonstrated that 95% of incident anemia occurred within the first 14 days, and that 97.4% did so while admitted to a high-acuity unit.[25] The risk of new onset vasospasm, a significant threat to morbidity and mortality in this population is highly unlikely to begin after 14 days but its duration may surpass this period.[19] A Screen Eligible period is essential to focus study resources on the group of patients most likely to be randomized, to capture the first occurrence of anemia (to *minimize* any exposure time below their allocated transfusion threshold) and to optimize the randomization rate. The study team will screen daily hemoglobin values (or more frequent as clinically indicated and/or as deemed by treating team) of Screen Eligible Patients.

Patients meeting eligibility criteria (or their substitute decision maker) will be approached for consent by the site research coordinator in accordance with standard local procedures as approved by each local REB and in accordance with Good Clinical Practice. A mixed consent model (a priori and deferred consent models), pending on local REB approval, will be used. A web-based randomization system maintained at the Coordinating Center will be used to allocate treatment assignments. Under the guidance of the site principal investigator or research coordinator, the participant's eligibility criteria will again be confirmed with a checklist using a

web interface. Upon meeting the randomization criteria, patients will be randomized in a 1:1 manner to either liberal (intervention) or restrictive (control) RBC transfusion strategy groups. A schedule of the random treatment allocations, stratified by center will be prepared by an independent biostatistician at the Coordinating Center. All investigative team members will remain blinded to the allocation schedules.

Intervention

Patients fulfilling the eligibility criteria will by randomized to either a liberal or restrictive RBC transfusion strategy.

Intervention Group: Liberal RBC Transfusion Strategy:

In this intervention group, an RBC transfusion will be triggered by a hemoglobin level of ≤100g/L over the first 21 days in hospital following aSAH.

Control Group: 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 in hospital following aSAH. RBC transfusion will not be mandatory under this threshold, "usual care" rather will prevail, and the decision to and timing of transfusion will be left to the discretion of the treating team.

Both Groups

All RBC transfusions will be a single unit unless the patient has an active blood loss associated with hemodynamic instability. In stable non-bleeding patients, a second unit of RBCs should only be given if a measured post-transfusion hemoglobin level remains below the patient's assigned threshold.

Justification of the two triggers

Intervention: Liberal RBC Transfusion Trigger (100g/L): Supported by:

a) Physiologic evidence that RBC transfusion increases oxygen delivery and cerebral tissue oxygen tension.[26–28]

b) Amongst SAH patients with hemoglobin <110g/L, compared to induced hypertension and fluid bolus, RBC transfusion was the only intervention demonstrated to significantly reduce (47%) the number of cerebral regions with low oxygen delivery per patient. Amongst those with low global oxygen delivery, RBC transfusion resulted in a significant larger rise in global oxygen delivery.[26]

c) A small physiologic study of aSAH patients (N=8) demonstrated stable cerebral blood flow, an increase in oxygen delivery and a decrease in the oxygen extraction fraction with an RBC transfusion at a hemoglobin level of <100 g/L.[29]

d) A hemoglobin level of <100g/L was associated with brain tissue hypoxia and metabolic distress compared to those with hemoglobin >100g/L.[30]

e) The maximum threshold hemoglobin to trigger RBC transfusion in the context of a study amongst the 531 intensivists, neurointensivists and neurosurgeons surveyed was 100g/L. [23]

Control: Restrictive RBC Transfusion Trigger (80g/L): Supported by:

a) In a survey of 531 practicing intensivists, neurointensivists and neurosurgeons in North America the median hemoglobin to trigger a transfusion ranged from 75 to 80g/L depending on SAH grade. [23]

b) Amongst practicing intensivists, neurointensivists and neurosurgeons the lowest acceptable threshold hemoglobin to trigger a RBC transfusion was 70g/L in >70% of respondents. [23]

c) A Canadian multi-center observational study (N=434) conducted in 4 academic centers in 2012 and 2013 completed by the SAHaRA study team demonstrated that the median pre-transfusion hemoglobin was 79g/L (IQR 74-93g/L).[31]

A transfusion trigger of 100g/L has previously been shown to be safe in an aSAH population.[18] The allocated transfusion strategy will be applied from the time of randomization to day 21 after the original bleed, death or hospital discharge, whichever comes first. The first 21 days following aSAH represents the period of greatest vulnerability to the direct consequences of aSAH, and the sequelae, including vasospasm, that follow.

Outcomes

Primary outcome

The primary feasibility endpoint is the number of patients randomized per center per month over the study period. We expect, amongst patients suffering from aSAH and anemia, 1.5 patients/month at each of 5 sites to be randomized into the trial. We reason that an optimal randomization rate of 1.5 participants/month/site and as low as 1 participant/month/site, will be necessary to demonstrate the feasibility of conducting the larger planned trial (Figure 2). This outcome is objective, readily measurable, and feasible based on data generated from a cohort study conducted by the authors.

Secondary outcomes

a) *Transfusion threshold adherence* will be described as the proportion of "per protocol" RBC transfusion *events*. A transfusion threshold event is defined as an occurrence which starts when a hemoglobin value is measured at or below the allocated threshold for the first time since the previous event and ends when one of the following occurs: 1) an RBC transfusion is

administered; or 2) a repeat hemoglobin is obtained above the allocated threshold within 24 hours of the original measure.

Transfusion threshold **non-adherence** will be considered to have occurred with any of the following: 1) an RBC transfusion occurs before a transfusion threshold is crossed; or 2) in the liberal arm, a transfusion is not given following a threshold crossing. Transfusion threshold non-adherence will be considered a *deviation* if: 1) the early transfusion occurs within 5 g/L above the allocated threshold (eg: ≤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 (ie: a transfusion does not occur for a Hb of 95-100 g/L). All other threshold event non-adherences that are greater or less than 5 g/L for the liberal threshold and greater than 5 g/L below the restrictive threshold will be considered a protocol violation. Transfusion outside of hemoglobin thresholds for symptomatic anemia or in the event of an active blood loss associated with hemodynamic instability, as defined by the treating team, will be recorded, but not considered a protocol violation. Details on non-adherence (date and hemoglobin level prior to transfusion) and reasons for non-adherence (e.g. physician preference, patient instability, active bleeding, safety concern) will be recorded.

b) *RBC transfusion protocol adherence:* The SAHaRA investigators recognize the importance of minimizing exposure time below the allocated transfusion threshold and thus every effort shall be put forth to administer the transfusion expeditiously. For the pilot we endeavor not to exceed 6 hours from transfusion threshold event to transfusion initiation, in keeping with revascularization time performance measures in stroke literature.[32,33] Median time (and interquartile range) to RBC transfusion will be described. Transfusion protocol adherence will be defined as the proportion of RBC transfusions that are initiated within 6 hours. 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 between 6 and 24 hours will be considered a protocol deviation and greater than 24 hours from the threshold event will be considered a violation.

c) *Clinical outcome ascertainment* will include ability to capture vital status at discharge, modified Rankin Scale (mRS) score at 6 and 12 months and the Functional Independence Measure (FIM) and the EuroQOL Quality of Life Scale (EQ5D) at 12 months. The mRS, FIM and EQ5D will be completed by assessors blinded to participant treatment allocation. Each of the outcome assessment measures have been selected because they examine different aspects of the 3 primary levels of body function and stroke rehabilitation (impairment, activity and participation)[34] and are specifically validated and recommended outcome measures in stroke research.[35] The mRS is used as the outcome measure over mortality as it includes a spectrum allowing consideration of severe disability and mortality together as both are highly clinically significant. Neurologic outcome as assessed by mRS is a common outcome in the aneurysmal SAH literature[9,18,36–39] and is readily interpretable in this community. It takes <15 minutes to administer, and can be completed using a structured interview[40–42] or as a telephone interview.[43] The FIM is a validated[44,45] tool consisting of 18 items that assesses 13 different motor and 5 cognitive tasks previously tested in stroke populations including aSAH,[44,46] and has an established minimal clinical important difference (MCID) in this population.[47] 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.[34] The EQ5D is a short and simple 2-

part questionnaire that may be self-administered, completed by interview or via a proxy respondent, and is used to value and describe health states.[34]

Baseline Characteristics, Co-Intervention, Outcome Assessment and Follow-up:

Important baseline characteristics (Table 1A) will be captured at time of enrolment for comparison between the 2 study groups to demonstrate the effectiveness of randomization. In this trial, patient management outside of RBC transfusion will be left to the discretion of the treating team and in accordance with practice guidelines[19] which will be made available to all participating centers and clinicians. All major co-interventions (eg: vasospasm, aneurysm and blood pressure management - Table 1B) will be carefully documented with daily record by the investigative team.

Table 1: Important baseline characteristics and co-interventions to be prospectively collected

A: Baseline characteristics (from time of enrolment and randomization)

Factor	Variable to capture
Age at enrolment[7,14,24,48,49]	Age in years
Sex[6]	Male or Female
History of CAD, HTN[6,49]	Present or not
SAH Clinical Severity [6,7,13,14,24,48,49]	WFNS score
SAH radiographic Severity[13,24,49]	Fisher Scale Score
Hydrocephalus[49]	Need for EVD
Aneurysm size and location[48]	Size (mm), artery involved
Method aneurysm secured[6,24,50]	Clip or coil or not secured
Presence of vasospasm[7,10,13,24,49]	Radiographic or clinical vasospasm*
Presence of cerebral infarct[5,48,49]	Cerebral infarct on pre-randomization imaging

CAD=coronary artery disease, EVD=external ventricular drain, HTN=hypertension, SAH=subarachnoid hemorrhage, WFNS=World Federation of Neurosurgeons, *radiographic vasospasm defined as a reduction of cerebral artery diameter on digital subtraction angiography and classified as mild (0-33% reduction), moderate (34-66% reduction) or severe (67-100% reduction) or by transcranial Doppler with a mean middle or anterior cerebral artery flow velocity of >200cm/s or an increase of >50cm/s/24h on repeated measures and a Lindegaard ratio of ≥3, clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of ≥2 points for ≥2 hours or new focal neurological deficit)

B: Co-Interventions

Co-Intervention		Variable to capture	Operationalization
Vasospasm*[7,10,13,48,49]	Vasospasm prophylaxis	Hyperdynamic therapy (prior to diagnosis of vasospasm)	-use of vasopressors to drive a target MAP>65mmHg
			-use of IV fluid infusions or regular boluses over maintenance
			-use of IV fluids to target specific hematocrit
		Magnesium (prior to diagnosis of vasospasm)	-use of magnesium IV infusion
		Chemical vasodilators (prior to diagnosis of vasospasm)	-use of infusion of vasodilator (IV) or any IA use (eg: milrinone, paperavine, CCB etc)
	Vasospasm treatment	Hyperdynamic therapy (after diagnosis of vasospasm)	-same criteria as above
		Magnesium	-same criteria as above
		Mechanical vasodilation	-use of balloon angioplasty or stent
		Chemical vasodilation	-use of infusion of vasodilator (IV) or any IA use (eg: milrinone, paperavine, CCB etc).
Definitive Aneurysm Management (if completed post randomization)[6,24]		Clip vs coil	-used or not
		Time to clip or coil	-minutes
Blood pressure management[31]		-daily use of vasopressor	-used or not
		-highest daily target MAP	-mmHg
Fever/temperature regulation[5,48]		-fever	-daily highest temperature

MAP=mean arterial pressure, IV=intravenous, IA=intra-arterial, CCB=calcium channel blocker, *radiographic vasospasm defined as a reduction of cerebral artery diameter on digital subtraction angiography and classified as mild (0-33% reduction), moderate (34-66% reduction) or severe (67-100% reduction) or by transcranial Doppler with a mean middle or anterior cerebral artery flow velocity of >200cm/s or an increase of >50cm/s/24h on repeated measures and a Lindegaard ratio of ≥3, clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of ≥2 points for ≥2 hours or new focal neurological deficit)

Descriptive metrics will be used to measure feasibility including the primary outcome of randomization rate. These data will be gathered prospectively at each study center by a trained and qualified study nurse or practitioner using a case report form. The number of eligible but not enrolled patients will be tracked, and reasons for non-enrollment will be recorded. Protocol adherence will be assessed prospectively by trained study personnel and all episodes of non-

adherence to protocol will be adjudicated by 3 members of the steering committee, blinded to clinical outcome. Protocol adherence will be reported as a ratio of total correct transfusion threshold events to a combination of total number of transfusion events (needed or not needed per protocol) and total number of missed transfusion non-adherence events. Feasibility of outcome assessment will be measured by the ability to obtain the defined outcome measures at the pre-specified time periods. The three outcome measurement instruments (mRS, FIM and EQ5D) will be implemented by a trained and qualified study coordinator blinded to the intervention according the defined schedule (Table 2). Vital status at discharge and adverse events will be captured using a case report form prospectively by the site investigator or the research coordinator.

Table 2: Schedule of assessments

Assessment:	Baseline:	Prospective – Daily	Hospital Discharge	6 months	12 months
Eligibility Criteria	X				
Recruitment	X				
Informed Consent	X				
Randomization	X				
Baseline Demographics	X				
Medical History	X				
Physical Exam including BP, O_2 sat, GCS	X	X	X		
Baseline labs	X				
aSAH clinical grade	X				
Neuro imaging (U/S, CT, MRI, Angio...)	X				
Vasospasm monitoring (CTA, U/S, angio...) and management	X	X	X		
Laboratory results		X	X		
Transfusion Requirements		X	X		
Co-intervention Log		X	X		
Adherence to treatment		X	X		
AE Review		X	X		
Neurologic outcome (mRS)			X	X	X

Functional Independence Measure (FIM)					X
EuroQOL Quality of Life Scale (EQ5D)					X

GCS: Glasgow Coma Score; U/S: ultrasound.

Ethics and Data Monitoring Body

The study protocol has been approved by the host center (Ottawa Health Science Network Research Ethics Board - OHSN-REB 20150433-01H). The **intervention and control** arm of the trial are part of usual care in many centers, and thus the research risk to participants is minimal. Safety considerations are addressed within the protocol, and allow for individualized care where needed.

A three-member Data Safety Monitoring Committee (DSMC) has been assembled and will oversee the progression of ascertaining the pilot objectives and all trial safety aspects according to a prescribed schedule, DSMC Charter and GCP reporting.

Sample Size

A sample size of 60 patients will allow us to evaluate enrolment rate averaging 1.5 patients per month per center with 5 centers over a 1-year study period. Based on our cohort study, we expect that 90 eligible patients will need to be screened into the study to achieve a randomized sample of 60 patients. Our sample size will also allow the demonstration of a protocol adherence rate of 90% with a 95% confidence interval of 82.4% to 97.6%.

Analytical Plan

a) **Descriptive Analyses:** Baseline characteristics and management data will be presented with means (continuous measures) or proportions (categorical or ordinal data) with 95% confidence intervals.

b) **Primary Outcome:** Using descriptive statistics, the median randomization rate (patients/month) overall and per center over the study duration will be calculated and reported with interquartile range. Only actual months where each center is actively recruiting patients will be considered in the analysis (i.e.: staggered start up across centers). Figure 2 demonstrates the effect of different randomization rates on study duration and hence feasibility. A rate of <1 patients/month per center will prompt a site review of the screening log to examine reasons for missed eligible patients and to discuss how to increase recruitment rate. Achieving our internal pilot primary objective of a randomization rate of 1.5 patients per month per center will allow us to complete the large trial in 3.5 years with 10 recruiting centers.

c) **Secondary Outcomes:** Secondary feasibility outcomes will be reported using descriptive statistics. Protocol adherence will be reported as a proportion as described above. Overall protocol adherence as well as adherence in the 2 individual study arms will be reported. Given the internal pilot design, with the plan to include these data in the large trial if no substantial changes to the protocol are made after the pilot trial, clinical outcomes will be described in aggregate using descriptive statistics.

Study Timeline

We estimate a study duration of 30 months. Study center identification is complete. Patient enrolment began in mid-October 2015 and will take 12 months per center to complete or 16 months total assuming a staggered start (to allow for different lead times for site preparation including contracts and REB approval). The last clinical outcome measure is thus expected at 28 months leaving 2 additional months for data cleaning and analysis for manuscript preparation.

DISCUSSION

The TRICC trial,[22] the first rigorous trial comparing different red blood cell transfusion thresholds in a critically ill patient population, remains significant today and continues to guide management of many ICU populations. However, several sub-populations were underrepresented (or not at all) in this study, such that the debate of optimal transfusion threshold continues to plague physicians at certain ICU bedsides. The neurocritically ill, specifically aneurysmal subarachnoid hemorrhage patients are such a population. The clinical importance of varied transfusion thresholds in aSAH has never been studied in a large and rigorous randomized trial. The only RCT used transfusion thresholds that differ significantly from stated current practice, and was not powered for clinically meaningful outcomes.[18] The need for quality evidence to guide transfusion practice in aSAH has been identified by many influential societies, editorials and practice guidelines.[15,19,20,51] The uncritical use of variable thresholds does not advance patient outcome or physician practice.

Accomplishing the feasibility objectives of this pilot trial will ensure the successful completion of the future large trial. Our multi-center design is essential to demonstrate feasibility of enrollment and randomization into the study and across centers. A 12-month enrollment period will enable us to determine the feasibility of recruitment at individual centers. Only an open label design is feasible in a RBC transfusion strategy trial given the inability to blind bedside clinicians to hemoglobin levels in the safe management of these patients. Similar open label trial designs have been successfully completed in RBC transfusion trials involving other patient populations.[22,52–54] Further, prospective randomized open-label blinded end-point (PROBE) designs have been used in multiple successful, practice-changing stroke trials.[55–57] We will demonstrate the feasibility of collecting the proposed clinical outcomes of the large RCT

(neurologic functional outcome using mRS at 6 months and 1 year, as well as the FIM and EQ5D at 1 year) by observing the same follow-up schedule.

The results of the SAHaRA internal pilot trial will directly inform the conduct of and guide the successful completion of the larger RCT. The SAHaRA trial will clarify the role of treating anemia with RBC transfusion in this unique and vulnerable patient population, and whether that impacts on functional outcome and mortality. We hypothesize an improvement in outcome with the treatment of anemia which, if substantiated, would dramatically change the management of these patients by intensivists, neurologists and neurosurgeons world-wide. A null result would provide the necessary evidence to the bedside clinician that a restrictive transfusion approach is safe and prevent the unnecessary risk imposed by blood product transfusion that regularly occurs.

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AUTHORS CONTRIBUTIONS

SE, LM, DAF, MC and AFT conceived the project idea. SE, LM, DAF, MC, AFT, LF, DG, AA, AHK, AT, CL, JS, SM, DD, AB, and GP all contributed substantially to the design of the trial and drafting of the protocol. SE created the first draft of this submission and all authors have provided critical review and approve of this final version.

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COMPETING INTERESTS

None.

FIGURE LEGEND

Figure 1: SAHaRA Trial Design

Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation of enrollment

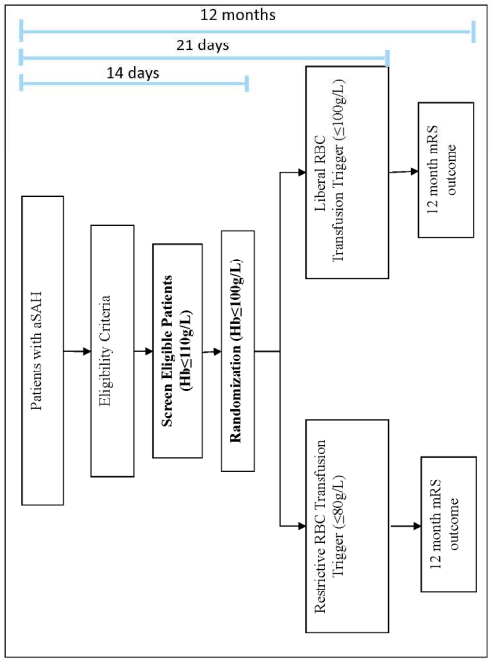

Figure 1: SAHaRA Trial Design
Figure 1
215x279mm (300 x 300 DPI)

Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation of enrollment
Figure 2
215x279mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	2, 26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15-16

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6, 9-11
	6b	Explanation for choice of comparators	9-11
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 8

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16-17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14,15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9, 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14, 15, 16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14-15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8, 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	27-28
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18, 20
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome (SAHaRA): A Pilot Randomized Controlled Trial Protocol

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Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome (SAHaRA): A Pilot Randomized Controlled Trial Protocol

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Trial Registry No.: NCT 02483351

Key Words: aneurysm, erythrocyte, subarachnoid hemorrhage, red blood cell transfusion, randomized controlled trial

Word count – Article: 3982 Abstract: 295

1. ABSTRACT

Introduction: Anemia is common in aneurysmal subarachnoid hemorrhage (aSAH) and is a potential critical modifiable factor affecting secondary injury. Despite physiologic evidence and management guidelines that support maintaining a higher hemoglobin level in patients with aSAH, current practice is one of a more restrictive approach to transfusion. The goal of this multicenter pilot trial is to determine the feasibility of successfully conducting an RBC transfusion trial in adult patients with acute aSAH and anemia (Hb≤100g/L), comparing a liberal transfusion strategy (Hb≤100g/L) to a restrictive strategy (Hb≤80g/L) on the combined rate of death and severe disability at 12 months.

Methods: Design: This is a multi-center open-label randomized controlled pilot trial at five academic tertiary care centers. **Population:** We are targeting adult aSAH patients within 14 days of their initial bleed and with anemia (Hb ≤110g/L). **Randomization:** Central computer-generated randomization, stratified by center, will be undertaken from the host center. Randomization into one of the two treatment arms will occur when the hemoglobin levels of eligible patients fall to ≤100g/L. **Intervention:** Patients will be randomly assigned to either a liberal (threshold: Hb≤100g/L) or a restrictive transfusion strategy (threshold: Hb≤80g/L). **Outcome:** Primary: Center randomization rate over the study period. Secondary: a) transfusion threshold adherence; b) study RBC transfusion protocol adherence; and c) outcome assessment including vital status at hospital discharge, modified Rankin Score at 6 and 12 months and functional independence measure and EuroQOL Quality of Life Scale scores at 12 months. Outcome measures will be reported in aggregate.

Ethics and Dissemination: The study protocol has been approved by the host center (OHSN-REB 20150433-01H). This study will determine the feasibility of conducting the large pragmatic

RCT comparing 2 RBC transfusion strategies examining the effect of a liberal strategy on 12-month outcome following aSAH. (Trial Registry No.: NCT 02483351)

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating illness caused by the spontaneous rupture of a weakened and enlarged artery in the brain. It affects a young population and is a significant cause of premature death and loss of potential life years, at a similar magnitude of ischemic stroke.[1] It is a common neurologic reason for intensive care unit (ICU) admission[2] and is associated with a mortality rate of about 35% in North America (range 20-70%).[3] Less than one third afflicted make a full recovery[4] and 20% of survivors experience significant morbidity[5] having an impact on daily living.

Anemia (hemoglobin [Hb] <100g/L) affects more than 50% of aSAH patients and is associated with worse clinical outcomes.[4,6–11] Preclinical studies in brain injury suggest that red blood cell (RBC) transfusion to treat anemia optimizes oxygen delivery in this specific setting.[4] However, RBC transfusions are not without risk and are a limited and expensive resource.[12] The limited evidence examining the association between RBC transfusion and clinical outcome from aSAH is derived from few observational studies with conflicting results and significant methodological limitations.[5,7,9,10,13–17] Only one small trial compared two transfusion targets in aSAH but was underpowered to examine clinically important outcomes.[18] Despite this absence of evidence, current aSAH management guidelines include a recommendation to *consider* RBC transfusion in anemic patients *at risk* for cerebral ischemia, but do not suggest transfusion thresholds to guide clinicians.[19,20] These recommendations are in contrast with evidence from randomized controlled trials (RCTs) in other critically ill adult and pediatric populations which support a more restrictive RBC transfusion approach.[21,22]

Although both the biological rationale and current recommendations for treating aSAH patients support a higher transfusion threshold (liberal strategy), the clinical evidence is lacking

to substantiate these recommendations. Current stated and observed practice from surveys[23] and our own observational work suggest a more restrictive approach to transfusion (lower hemoglobin); similar to other critical care patients. However, unlike other critically ill patients, brain injury and the sequelae that follow (e.g.: vasospasm and delayed cerebral ischemia) may make these patients more susceptible to the decreased oxygen delivery associated with a lower transfusion threshold. Considering this obvious paradox and confliction, there is pressing need to generate high-quality evidence to guide clinical RBC transfusion practices in aSAH. The clinical impact 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 (www.ccctg.ca), we aim to conduct such an RCT comparing two RBC transfusion strategies in adult patients with aSAH powered for clinically relevant outcomes. To inform and justify our large trial, we are conducting a pilot RCT to assess feasibility and strengthen the design of the large-scale trial.

METHODS AND ANALYSIS

Study Design

The Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome: A Pilot Randomized Controlled Trial (SAHaRA Pilot Trial) is a Canadian multicenter (5) open-label randomized controlled pilot trial in patients with an acute aSAH. To reduce bias from the open-label design, outcome assessors will be blinded to the treatment assignments.

Patient Population

To facilitate randomization into the pilot trial, a subset of patients most likely to meet randomization criteria will be identified (Screen Eligible Patients). To be screened eligible for enrolment, patients must meet all inclusion criteria and no exclusion criteria.

Inclusion Criteria:

1. Age ≥18 years old at time of presentation
2. First ever episode aSAH
3. Confirmed aSAH diagnosis: as confirmed by treating neurosurgeon or neuro-interventionalist and supported by blood in subarachnoid space (demonstrated on cranial imaging or cerebrospinal fluid positive for xanthochromia) that is the result of a ruptured saccular aneurysm (confirmed by cranial imaging – computed tomography, magnetic resonance or catheter angiogram)
4. Incident Hb ≤110g/L within 14 days following aSAH (defined by first day of hospital presentation)

Exclusion Criteria:

1. Physician and or next of kin decision to withdraw/withhold critical 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 causes other than saccular aneurysm rupture including mycotic, traumatic and dissecting aneurysms, and aneurysms associated with arteriovenous malformations

Our exclusion criteria are in place to prevent enrolling patients who: 1) would not benefit from the intervention; 2) object to the intervention; and/or 3) have sustained a bleed due to mechanistically different causes whose pathophysiological properties are not necessarily shared with aSAH.

Screen eligible patients who experience an incident Hb ≤100 g/L within 14 days following aSAH will be randomized.

Randomization and Allocation Concealment:

Figure 1 provides a schematic description of the trial design. Local research coordinators will screen each patient admitted to either the intensive care unit, intermediate care unit or step-down unit (where applicable) or neurosurgical inpatient unit in the setting of aSAH for up to 14 days after the qualifying bleed. Enrolment and randomization over 14 days is necessary as previous work has demonstrated that the negative effect on outcome was most pronounced in patients with anemia between days 6 and 11.[24] Further, our observational study demonstrated that 95% of incident anemia occurred within the first 14 days, and that 97.4% did so while admitted to a high-acuity unit.[25] The risk of new onset vasospasm, a significant threat to morbidity and mortality in this population is highly unlikely to begin after 14 days but its duration may surpass this period.[19] A Screen Eligible period is essential to focus study resources on the group of patients most likely to be randomized, to capture the first occurrence of anemia (to *minimize* any exposure time below their allocated transfusion threshold) and to optimize the randomization rate. The study team will screen daily hemoglobin values (or more frequent as clinically indicated and/or as deemed by treating team) of Screen Eligible Patients.

Patients meeting eligibility criteria (or their substitute decision maker) will be approached for consent by the site research coordinator in accordance with standard local procedures as approved by each local REB and in accordance with Good Clinical Practice. A mixed consent model (a priori and deferred consent models), pending on local REB approval, will be used. A web-based randomization system maintained at the Coordinating Center will be used to allocate treatment assignments. Under the guidance of the site principal investigator or research coordinator, the participant's eligibility criteria will again be confirmed with a checklist using a

web interface. Upon meeting the randomization criteria, patients will be randomized in a 1:1 manner to either liberal (intervention) or restrictive (control) RBC transfusion strategy groups. A schedule of the random treatment allocations, stratified by center will be prepared by an independent biostatistician at the Coordinating Center. All investigative team members will remain blinded to the allocation schedules.

Intervention

Patients fulfilling the eligibility criteria will by randomized to either a liberal or restrictive RBC transfusion strategy.

Intervention Group: Liberal RBC Transfusion Strategy:

In this intervention group, an RBC transfusion will be triggered by a hemoglobin level of ≤100g/L over the first 21 days in hospital following aSAH.

Control Group: 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 in hospital following aSAH. RBC transfusion will not be mandatory under this threshold, "usual care" rather will prevail, and the decision to and timing of transfusion will be left to the discretion of the treating team.

Both Groups

All RBC transfusions will be a single unit unless the patient has an active blood loss associated with hemodynamic instability. In stable non-bleeding patients, a second unit of RBCs should only be given if a measured post-transfusion hemoglobin level remains below the patient's assigned threshold.

Justification of the two triggers

Intervention: Liberal RBC Transfusion Trigger (100g/L): Supported by:

a) Physiologic evidence that RBC transfusion increases oxygen delivery and cerebral tissue oxygen tension.[26–28]

b) Amongst SAH patients with hemoglobin <110g/L, compared to induced hypertension and fluid bolus, RBC transfusion was the only intervention demonstrated to significantly reduce (47%) the number of cerebral regions with low oxygen delivery per patient. Amongst those with low global oxygen delivery, RBC transfusion resulted in a significant larger rise in global oxygen delivery.[26]

c) A small physiologic study of aSAH patients (N=8) demonstrated stable cerebral blood flow, an increase in oxygen delivery and a decrease in the oxygen extraction fraction with an RBC transfusion at a hemoglobin level of <100 g/L.[29]

d) A hemoglobin level of <100g/L was associated with brain tissue hypoxia and metabolic distress compared to those with hemoglobin >100g/L.[30]

e) The maximum threshold hemoglobin to trigger RBC transfusion in the context of a study amongst the 531 intensivists, neurointensivists and neurosurgeons surveyed was 100g/L. [23]

Control: Restrictive RBC Transfusion Trigger (80g/L): Supported by:

a) In a survey of 531 practicing intensivists, neurointensivists and neurosurgeons in North America the median hemoglobin to trigger a transfusion ranged from 75 to 80g/L depending on SAH grade. [23]

b) Amongst practicing intensivists, neurointensivists and neurosurgeons the lowest acceptable threshold hemoglobin to trigger a RBC transfusion was 70g/L in >70% of respondents. [23]

c) A Canadian multi-center observational study (N=434) conducted in 4 academic centers in 2012 and 2013 completed by the SAHaRA study team demonstrated that the median pre-transfusion hemoglobin was 79g/L (IQR 74-93g/L).[31]

A transfusion trigger of 100g/L has previously been shown to be safe in an aSAH population.[18] The allocated transfusion strategy will be applied from the time of randomization to day 21 after the original bleed, death or hospital discharge, whichever comes first. The first 21 days following aSAH represents the period of greatest vulnerability to the direct consequences of aSAH, and the sequelae, including vasospasm, that follow.

Outcomes

Primary outcome

The primary feasibility endpoint is the number of patients randomized per center per month over the study period. We expect, amongst patients suffering from aSAH and anemia, 1.5 patients/month at each of 5 sites to be randomized into the trial. We reason that an optimal randomization rate of 1.5 participants/month/site and as low as 1 participant/month/site, will be necessary to demonstrate the feasibility of conducting the larger planned trial (Figure 2). This outcome is objective, readily measurable, and feasible based on data generated from a cohort study conducted by the authors.

Secondary outcomes

a) *Transfusion threshold adherence* will be described as the proportion of "per protocol" RBC transfusion *events*. A transfusion threshold event is defined as an occurrence which starts when a hemoglobin value is measured at or below the allocated threshold for the first time since the previous event and ends when one of the following occurs: 1) an RBC transfusion is

administered; or 2) a repeat hemoglobin is obtained above the allocated threshold within 24 hours of the original measure.

Transfusion threshold **non-adherence** will be considered to have occurred with any of the following: 1) an RBC transfusion occurs before a transfusion threshold is crossed; or 2) in the liberal arm, a transfusion is not given following a threshold crossing. Transfusion threshold non-adherence will be considered a *deviation* if: 1) the early transfusion occurs within 5 g/L above the allocated threshold (eg: ≤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 (ie: a transfusion does not occur for a Hb of 95-100 g/L). All other threshold event non-adherences that are greater or less than 5 g/L for the liberal threshold and greater than 5 g/L below the restrictive threshold will be considered a protocol violation. Transfusion outside of hemoglobin thresholds for symptomatic anemia or in the event of an active blood loss associated with hemodynamic instability, as defined by the treating team, will be recorded, but not considered a protocol violation. Details on non-adherence (date and hemoglobin level prior to transfusion) and reasons for non-adherence (e.g. physician preference, patient instability, active bleeding, safety concern) will be recorded.

b) *RBC transfusion protocol adherence:* The SAHaRA investigators recognize the importance of minimizing exposure time below the allocated transfusion threshold and thus every effort shall be put forth to administer the transfusion expeditiously. For the pilot we endeavor not to exceed 6 hours from transfusion threshold event to transfusion initiation, in keeping with revascularization time performance measures in stroke literature.[32,33] Median time (and interquartile range) to RBC transfusion will be described. Transfusion protocol adherence will be defined as the proportion of RBC transfusions that are initiated within 6 hours. 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 between 6 and 24 hours will be considered a protocol deviation and greater than 24 hours from the threshold event will be considered a violation.

c) *Clinical outcome ascertainment* will include ability to capture vital status at discharge, modified Rankin Scale (mRS) score at 6 and 12 months and the Functional Independence Measure (FIM) and the EuroQOL Quality of Life Scale (EQ5D) at 12 months. The mRS, FIM and EQ5D will be completed by assessors blinded to participant treatment allocation. Each of the outcome assessment measures have been selected because they examine different aspects of the 3 primary levels of body function and stroke rehabilitation (impairment, activity and participation)[34] and are specifically validated and recommended outcome measures in stroke research.[35] The mRS is used as the outcome measure over mortality as it includes a spectrum allowing consideration of severe disability and mortality together as both are highly clinically significant. Neurologic outcome as assessed by mRS is a common outcome in the aneurysmal SAH literature[9,18,36–39] and is readily interpretable in this community. It takes <15 minutes to administer, and can be completed using a structured interview[40–42] or as a telephone interview.[43] The FIM is a validated[44,45] tool consisting of 18 items that assesses 13 different motor and 5 cognitive tasks previously tested in stroke populations including aSAH,[44,46] and has an established minimal clinical important difference (MCID) in this population.[47] 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.[34] The EQ5D is a short and simple 2-

part questionnaire that may be self-administered, completed by interview or via a proxy respondent, and is used to value and describe health states.[34]

Baseline Characteristics, Co-Intervention, Outcome Assessment and Follow-up:

Important baseline characteristics (Table 1A) will be captured at time of enrolment for comparison between the 2 study groups to demonstrate the effectiveness of randomization. In this trial, patient management outside of RBC transfusion will be left to the discretion of the treating team and in accordance with practice guidelines[19] which will be made available to all participating centers and clinicians. All major co-interventions (eg: vasospasm, aneurysm and blood pressure management - Table 1B) will be carefully documented with daily record by the investigative team. Other clinical outcomes being collected include incidence and severity of vasospasm, incidence of cerebral infarction not directly related to complication from securing aneurysm, need for intubation, tracheostomy, percutaneous gastrostomy tube and/or ventricular shunt and ICU and hospital lengths of stay.

Table 1: Important baseline characteristics and co-interventions to be prospectively collected

A: Baseline characteristics (from time of enrolment and randomization)

Factor	Variable to capture
Age at enrolment[7,14,24,48,49]	Age in years
Sex[6]	Male or Female
History of CAD, HTN[6,49]	Present or not
SAH Clinical Severity [6,7,13,14,24,48,49]	WFNS score
SAH radiographic Severity[13,24,49]	Modified Fisher Scale Score
Hydrocephalus[49]	Need for EVD
Aneurysm size and location[48]	Size (mm), artery involved
Method aneurysm secured[6,24,50]	Clip or coil or not secured
Presence of vasospasm[7,10,13,24,49]	Radiographic or clinical vasospasm*
Presence of cerebral infarct[5,48,49]	Cerebral infarct on pre-randomization imaging

CAD=coronary artery disease, EVD=external ventricular drain, HTN=hypertension, SAH=subarachnoid hemorrhage, WFNS=World Federation of Neurosurgeons, *radiographic vasospasm defined as a reduction of cerebral artery diameter on digital subtraction angiography and classified as mild (0-33% reduction), moderate (34-66% reduction) or severe (67-100% reduction) or by transcranial Doppler with a mean middle or anterior cerebral artery flow velocity of >200cm/s or an increase of >50cm/s/24h on repeated measures and a Lindegaard ratio of ≥3, clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of ≥2 points for ≥2 hours or new focal neurological deficit)

B: Co-Interventions

Co-Intervention		Variable to capture	Operationalization
Vasospasm*[7,10,13,48,49]	Vasospasm prophylaxis	Hyperdynamic therapy (prior to diagnosis of vasospasm)	-use of vasopressors to drive a target MAP>65mmHg
			-use of IV fluid infusions or regular boluses over maintenance
			-use of IV fluids to target specific hematocrit
		Magnesium (prior to diagnosis of vasospasm)	-use of magnesium IV infusion
		Chemical vasodilators (prior to diagnosis of vasospasm)	-use of infusion of vasodilator (IV) or any IA use (eg: milrinone, paperavine, CCB etc)
	Vasospasm treatment	Hyperdynamic therapy (after diagnosis of vasospasm)	-same criteria as above
		Magnesium	-same criteria as above
		Mechanical vasodilation	-use of balloon angioplasty or stent
		Chemical vasodilation	-use of infusion of vasodilator (IV) or any IA use (eg: milrinone, paperavine, CCB etc).
Definitive Aneurysm Management (if completed post randomization)[6,24]		Clip vs coil	-used or not
		Time to clip or coil	-minutes
Blood pressure management[31]		-daily use of vasopressor	-used or not
		-highest daily target MAP	-mmHg
Fever/temperature regulation[5,48]		-fever	-daily highest temperature

MAP=mean arterial pressure, IV=intravenous, IA=intra-arterial, CCB=calcium channel blocker, *radiographic vasospasm defined as a reduction of cerebral artery diameter on digital subtraction angiography and classified as mild (0-33% reduction), moderate (34-66% reduction) or severe (67-100% reduction) or by transcranial Doppler with a mean middle or anterior cerebral artery flow velocity of >200cm/s or an increase of >50cm/s/24h on repeated measures and a Lindegaard ratio of ≥3, clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of ≥2 points for ≥2 hours or new focal neurological deficit)

Descriptive metrics will be used to measure feasibility including the primary outcome of randomization rate. These data will be gathered prospectively at each study center by a trained and qualified study nurse or practitioner using a case report form. The number of eligible but not enrolled patients will be tracked, and reasons for non-enrollment will be recorded. Protocol adherence will be assessed prospectively by trained study personnel and all episodes of non-

adherence to protocol will be adjudicated by 3 members of the steering committee, blinded to clinical outcome. Protocol adherence will be reported as a ratio of total correct transfusion threshold events to a combination of total number of transfusion events (needed or not needed per protocol) and total number of missed transfusion non-adherence events. Feasibility of outcome assessment will be measured by the ability to obtain the defined outcome measures at the pre-specified time periods. The three outcome measurement instruments (mRS, FIM and EQ5D) will be implemented by a trained and qualified study coordinator blinded to the intervention according the defined schedule (Table 2). Vital status at discharge and adverse events will be captured using a case report form prospectively by the site investigator or the research coordinator.

Table 2: Schedule of assessments

Assessment:	Baseline:	Prospective – Daily	Hospital Discharge	6 months	12 months
Eligibility Criteria	X				
Recruitment	X				
Informed Consent	X				
Randomization	X				
Baseline Demographics	X				
Medical History	X				
Physical Exam including BP, O_2 sat, GCS	X	X	X		
Baseline labs	X				
aSAH clinical grade	X				
Neuro imaging (U/S, CT, MRI, Angio...)	X				
Vasospasm monitoring (CTA, U/S, angio...) and management	X	X	X		
Laboratory results		X	X		
Transfusion Requirements		X	X		
Co-intervention Log		X	X		
Adherence to treatment		X	X		
AE Review		X	X		
Neurologic outcome (mRS)			X	X	X

Functional Independence Measure (FIM)					X
EuroQOL Quality of Life Scale (EQ5D)					X

GCS: Glasgow Coma Score; U/S: ultrasound.

Ethics and Data Monitoring Body

The study protocol has been approved by the host center (Ottawa Health Science Network Research Ethics Board - OHSN-REB 20150433-01H). The **intervention and control** arm of the trial are part of usual care in many centers, and thus the research risk to participants is minimal. Safety considerations are addressed within the protocol, and allow for individualized care where needed. In addition to potentially intervention-related adverse event reporting, pre-defined expected adverse events will be prospectively monitored and include acute respiratory distress syndrome, cardiovascular failure, cardiac ischemia/infarction, venous thromboembolic events, septic shock, hospital acquired infections and transfusion reactions.

A three-member Data Safety Monitoring Committee (DSMC) has been assembled and will oversee the progression of ascertaining the pilot objectives and all trial safety aspects according to a prescribed schedule, DSMC Charter and GCP reporting.

Sample Size

A sample size of 60 patients will allow us to evaluate enrolment rate averaging 1.5 patients per month per center with 5 centers over a 1-year study period. Based on our cohort study, we expect that 90 eligible patients will need to be screened into the study to achieve a randomized sample of 60 patients (that is more than 2/3 of patients with a hemoglobin of ≤110g/L had a nadir of 100g/L or less). All 5 proposed pilot trial sites are academic tertiary care centres with approximately 60-120 aSAH admissions per year. Our sample size will also allow the

demonstration of a protocol adherence rate of 90% with a 95% confidence interval of 82.4% to 97.6%.

Analytical Plan

a) **Descriptive Analyses:** Baseline characteristics and management data will be presented with means (continuous measures) or proportions (categorical or ordinal data) with 95% confidence intervals.

b) **Primary Outcome:** Using descriptive statistics, the median randomization rate (patients/month) overall and per center over the study duration will be calculated and reported with interquartile range. Only actual months where each center is actively recruiting patients will be considered in the analysis (i.e.: staggered start up across centers). Figure 2 demonstrates the effect of different randomization rates on study duration and hence feasibility. A rate of <1 patients/month per center will prompt a site review of the screening log to examine reasons for missed eligible patients and to discuss how to increase recruitment rate. Achieving our internal pilot primary objective of a randomization rate of 1.5 patients per month per center will allow us to complete the large trial in 3.5 years with 10 recruiting centers.

c) **Secondary Outcomes:** Secondary feasibility outcomes will be reported using descriptive statistics. Protocol adherence will be reported as a proportion as described above. Overall protocol adherence as well as adherence in the 2 individual study arms will be reported. Given the internal pilot design, with the plan to include these data in the large trial if no substantial changes to the protocol are made after the pilot trial, clinical outcomes will be described in aggregate using descriptive statistics.

Study Timeline

We estimate a study duration of 30 months. Study center identification is complete. Patient enrolment began in mid-October 2015 and will take 12 months per center to complete or 16 months total assuming a staggered start (to allow for different lead times for site preparation including contracts and REB approval). The last clinical outcome measure is thus expected at 28 months leaving 2 additional months for data cleaning and analysis for manuscript preparation.

DISCUSSION

The TRICC trial,[22] the first rigorous trial comparing different red blood cell transfusion thresholds in a critically ill patient population, remains significant today and continues to guide management of many ICU populations. However, several sub-populations were underrepresented (or not at all) in this study, such that the debate of optimal transfusion threshold continues to plague physicians at certain ICU bedsides. The neurocritically ill, specifically aneurysmal subarachnoid hemorrhage patients are such a population. The clinical importance of varied transfusion thresholds in aSAH has never been studied in a large and rigorous randomized trial. The only RCT used transfusion thresholds that differ significantly from stated current practice, and was not powered for clinically meaningful outcomes.[18] The need for quality evidence to guide transfusion practice in aSAH has been identified by many influential societies, editorials and practice guidelines.[15,19,20,51] The uncritical use of variable thresholds does not advance patient outcome or physician practice.

Accomplishing the feasibility objectives of this pilot trial will ensure the successful completion of the future large trial. A pilot trial powered to feasibility outcomes is the essential initial step in the preparation for and eventual successful completion of the more costly larger trial, powered to

clinically relevant outcomes.[52] Our multi-center design is essential to demonstrate feasibility of enrollment and randomization into the study and across centers. A 12-month enrollment period will enable us to determine the feasibility of recruitment at individual centers. Only an open label design is feasible in a RBC transfusion strategy trial given the inability to blind bedside clinicians to hemoglobin levels in the safe management of these patients. Similar open label trial designs have been successfully completed in RBC transfusion trials involving other patient populations.[22,53–55] Further, prospective randomized open-label blinded end-point (PROBE) designs have been used in multiple successful, practice-changing stroke trials.[56–58] To minimize potential bias imposed from open label treatments, our clinical outcome measures will be completed by a blinded assessor who has not been involved in patient management and is unaware of treatment assignment. We will demonstrate the feasibility of collecting the proposed clinical outcomes of the large RCT (neurologic functional outcome using mRS at 6 months and 1 year, as well as the FIM and EQ5D at 1 year) by observing the same follow-up schedule.

The results of the SAHaRA internal pilot trial will directly inform the conduct of and guide the successful completion of the larger RCT. The SAHaRA trial will clarify the role of treating anemia with RBC transfusion in this unique and vulnerable patient population, and whether that impacts on functional outcome and mortality. We hypothesize an improvement in outcome with the treatment of anemia which, if substantiated, would dramatically change the management of these patients by intensivists, neurologists and neurosurgeons world-wide. A null result would provide the necessary evidence to the bedside clinician that a restrictive transfusion approach is safe and prevent the unnecessary risk imposed by blood product transfusion that regularly occurs.

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AUTHORS CONTRIBUTIONS

SE, LM, DAF, MC and AFT conceived the project idea. SE, LM, DAF, MC, AFT, LF, DG, AA, AHK, AT, CL, JS, SM, DD, AB, and GP all contributed substantially to the design of the trial and drafting of the protocol. SE created the first draft of this submission and all authors have provided critical review and approve of this final version.

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COMPETING INTERESTS

None.

FIGURE LEGEND

Figure 1: SAHaRA Trial Design

Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation of enrollment

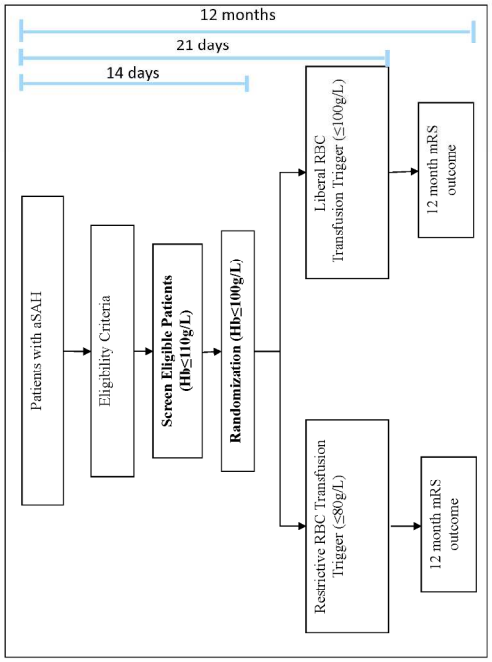

Figure 1: SAHaRA Trial Design
Figure 1
215x279mm (300 x 300 DPI)

Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation of enrollment
Figure 2
215x279mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	2, 26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15-16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6, 9-11
	6b	Explanation for choice of comparators	9-11
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	16-17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14,15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9, 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14, 15, 16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14-15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8, 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	27-28
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18, 20
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome (SAHaRA): A Pilot Randomized Controlled Trial Protocol

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Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome (SAHaRA): A Pilot Randomized Controlled Trial Protocol

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Trial Registry No.: NCT 02483351 (clinicaltrials.gov registered June 25, 2015)

Key Words: aneurysm, erythrocyte, subarachnoid hemorrhage, red blood cell transfusion, randomized controlled trial

Word count – Article: 3982 Abstract: 295

ABSTRACT

Introduction: Anemia is common in aneurysmal subarachnoid hemorrhage (aSAH) and is a potential critical modifiable factor affecting secondary injury. Despite physiologic evidence and management guidelines that support maintaining a higher hemoglobin level in patients with aSAH, current practice is one of a more restrictive approach to transfusion. The goal of this multicenter pilot trial is to determine the feasibility of successfully conducting an RBC transfusion trial in adult patients with acute aSAH and anemia (Hb≤100g/L), comparing a liberal transfusion strategy (Hb≤100g/L) to a restrictive strategy (Hb≤80g/L) on the combined rate of death and severe disability at 12 months.

Methods: Design: This is a multi-center open-label randomized controlled pilot trial at five academic tertiary care centers. **Population:** We are targeting adult aSAH patients within 14 days of their initial bleed and with anemia (Hb ≤110g/L). **Randomization:** Central computer-generated randomization, stratified by center, will be undertaken from the host center. Randomization into one of the two treatment arms will occur when the hemoglobin levels of eligible patients fall to ≤100g/L. **Intervention:** Patients will be randomly assigned to either a liberal (threshold: Hb≤100g/L) or a restrictive transfusion strategy (threshold: Hb≤80g/L). **Outcome:** Primary: Center randomization rate over the study period. Secondary: a) transfusion threshold adherence; b) study RBC transfusion protocol adherence; and c) outcome assessment including vital status at hospital discharge, modified Rankin Score at 6 and 12 months and functional independence measure and EuroQOL Quality of Life Scale scores at 12 months. Outcome measures will be reported in aggregate.

Ethics and Dissemination: The study protocol has been approved by the host center (OHSN-REB 20150433-01H). This study will determine the feasibility of conducting the large pragmatic

RCT comparing 2 RBC transfusion strategies examining the effect of a liberal strategy on 12-month outcome following aSAH. (Trial Registry No.: NCT 02483351)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Rigorous trial methodology to evaluate the feasibility of conducting a larger trial to establish optimal red blood cell transfusion thresholds in patients with aneurysmal subarachnoid hemorrhage
- The multi-center pragmatic design strengthens future results and generalizability
- To minimize any potential bias from the necessary open-label design, collection of co-interventions and blinded outcome-assessment are being undertaken
- The pilot trial was not designed to test clinically relevant outcomes

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating illness caused by the spontaneous rupture of a weakened and enlarged artery in the brain. It affects a young population and is a significant cause of premature death and loss of potential life years, at a similar magnitude of ischemic stroke.[1] It is a common neurologic reason for intensive care unit (ICU) admission[2] and is associated with a mortality rate of about 35% in North America (range 20-70%).[3] Less than one third afflicted make a full recovery[4] and 20% of survivors experience significant morbidity[5] having an impact on daily living.

Anemia (hemoglobin [Hb] <100g/L) affects more than 50% of aSAH patients and is associated with worse clinical outcomes.[4,6–11] Preclinical studies in brain injury suggest that red blood cell (RBC) transfusion to treat anemia optimizes oxygen delivery in this specific setting.[4] However, RBC transfusions are not without risk and are a limited and expensive resource.[12] The limited evidence examining the association between RBC transfusion and clinical outcome from aSAH is derived from few observational studies with conflicting results and significant methodological limitations.[5,7,9,10,13–17] Only one small trial compared two transfusion targets in aSAH but was underpowered to examine clinically important outcomes.[18] Despite this absence of evidence, current aSAH management guidelines include a recommendation to *consider* RBC transfusion in anemic patients *at risk* for cerebral ischemia, but do not suggest transfusion thresholds to guide clinicians.[19,20] These recommendations are in contrast with evidence from randomized controlled trials (RCTs) in other critically ill adult and pediatric populations which support a more restrictive RBC transfusion approach.[21,22]

Although both the biological rationale and current recommendations for treating aSAH patients support a higher transfusion threshold (liberal strategy), the clinical evidence is lacking

to substantiate these recommendations. Current stated and observed practice from surveys[23] and our own observational work suggest a more restrictive approach to transfusion (lower hemoglobin); similar to other critical care patients. However, unlike other critically ill patients, brain injury and the sequelae that follow (e.g.: vasospasm and delayed cerebral ischemia) may make these patients more susceptible to the decreased oxygen delivery associated with a lower transfusion threshold. Considering this obvious paradox and confliction, there is pressing need to generate high-quality evidence to guide clinical RBC transfusion practices in aSAH. The clinical impact 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 (www.ccctg.ca), we aim to conduct such an RCT comparing two RBC transfusion strategies in adult patients with aSAH powered for clinically relevant outcomes. To inform and justify our large trial, we are conducting a pilot RCT to assess feasibility and strengthen the design of the large-scale trial.

METHODS AND ANALYSIS

Study Design

The Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome: A Pilot Randomized Controlled Trial (SAHaRA Pilot Trial) is a multicenter open-label randomized controlled pilot trial in patients with an acute aSAH at 5 Canadian academic tertiary care hospitals. To reduce bias from the open-label design, outcome assessors will be blinded to the treatment assignments.

Objectives

Primary Objective: To evaluate the feasibility of reaching an optimal randomization rate of at least 1 patient per month per center over the pilot trial period.

Secondary Objectives:1) To evaluate the feasibility of obtaining: a) at least 90% adherence to the allocated study transfusion thresholds; b) at least 90% adherence to the study RBC transfusion protocol; and c) ≥95% clinical outcomes measures (modified Rankin Scale [mRS], Functional Independence Measure [FIM] and EuroQOL Quality of Life Scale [EQ5D]) at 6 and 12 months.

Patient Population

To facilitate randomization into the pilot trial, a subset of patients most likely to meet randomization criteria will be identified (Screen Eligible Patients). To be screened eligible for enrolment, patients must meet all inclusion criteria and no exclusion criteria.

Inclusion Criteria:

1. Age ≥18 years old at time of presentation
2. First ever episode aSAH
3. Confirmed aSAH diagnosis: as confirmed by treating neurosurgeon or neuro-interventionalist and supported by blood in subarachnoid space (demonstrated on cranial imaging or cerebrospinal fluid positive for xanthochromia) that is the result of a ruptured saccular aneurysm (confirmed by cranial imaging – computed tomography, magnetic resonance or catheter angiogram)
4. Incident Hb ≤110g/L within 14 days following aSAH (defined by first day of hospital presentation)

Exclusion Criteria:

1. Physician and or next of kin decision to withdraw/withhold critical 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 causes other than saccular aneurysm rupture including mycotic, traumatic and dissecting aneurysms, and aneurysms associated with arteriovenous malformations

Our exclusion criteria are in place to prevent enrolling patients who: 1) would not benefit from the intervention; 2) object to the intervention; and/or 3) have sustained a bleed due to mechanistically different causes whose pathophysiological properties are not necessarily shared with aSAH.

Screen eligible patients who experience an incident Hb ≤100 g/L within 14 days following aSAH will be randomized.

Randomization and Allocation Concealment:

Figure 1 provides a schematic description of the trial design. Local research coordinators will screen each patient admitted to either the intensive care unit, intermediate care unit or step-down unit (where applicable) or neurosurgical inpatient unit in the setting of aSAH for up to 14 days after the qualifying bleed. Enrolment and randomization over 14 days is necessary as previous work has demonstrated that the negative effect on outcome was most pronounced in patients with anemia between days 6 and 11.[24] Further, our observational study demonstrated that 95% of incident anemia occurred within the first 14 days, and that 97.4% did so while admitted to a high-acuity unit.[25] The risk of new onset vasospasm, a significant threat to morbidity and mortality in this population is highly unlikely to begin after 14 days but its duration may surpass this period.[19] A Screen Eligible period is essential to focus study resources on the group of patients most likely to be randomized, to capture the first occurrence of anemia (to *minimize* any exposure time below their allocated transfusion threshold) and to optimize the randomization rate. The study team will screen daily hemoglobin values (or more frequent as clinically indicated and/or as deemed by treating team) of Screen Eligible Patients.

Patients meeting eligibility criteria (or their substitute decision maker) will be approached for consent by the site research coordinator in accordance with standard local procedures as approved by each local REB and in accordance with Good Clinical Practice. A mixed consent model (a priori and deferred consent models), pending on local REB approval, will be used. A web-based randomization system maintained at the Coordinating Center will be used to allocate treatment assignments. Under the guidance of the site principal investigator or research coordinator, the participant's eligibility criteria will again be confirmed with a checklist using a web interface. Upon meeting the randomization criteria, patients will be randomized in a 1:1 manner to either liberal (intervention) or restrictive (control) RBC transfusion strategy groups. A schedule of the random treatment allocations, stratified by center will be prepared by an independent biostatistician at the Coordinating Center. All investigative team members will remain blinded to the allocation schedules.

Intervention

Patients fulfilling the eligibility criteria will by randomized to either a liberal or restrictive RBC transfusion strategy.

Intervention Group: Liberal RBC Transfusion Strategy:

In this intervention group, an RBC transfusion will be triggered by a hemoglobin level of ≤100g/L over the first 21 days in hospital following aSAH.

Control Group: 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 in hospital following aSAH. RBC transfusion will not be mandatory under this threshold, "usual care" rather will prevail, and the decision to and timing of transfusion will be left to the discretion of the treating team.

Both Groups

All RBC transfusions will be a single unit unless the patient has an active blood loss associated with hemodynamic instability. In stable non-bleeding patients, a second unit of RBCs should only be given if a measured post-transfusion hemoglobin level remains below the patient's assigned threshold.

Justification of the two triggers

Intervention: Liberal RBC Transfusion Trigger (100g/L): Supported by:

a) Physiologic evidence that RBC transfusion increases oxygen delivery and cerebral tissue oxygen tension.[26–28]

b) Amongst SAH patients with hemoglobin <110g/L, compared to induced hypertension and fluid bolus, RBC transfusion was the only intervention demonstrated to significantly reduce (47%) the number of cerebral regions with low oxygen delivery per patient. Amongst those with low global oxygen delivery, RBC transfusion resulted in a significant larger rise in global oxygen delivery.[26]

c) A small physiologic study of aSAH patients (N=8) demonstrated stable cerebral blood flow, an increase in oxygen delivery and a decrease in the oxygen extraction fraction with an RBC transfusion at a hemoglobin level of <100 g/L.[29]

d) A hemoglobin level of <100g/L was associated with brain tissue hypoxia and metabolic distress compared to those with hemoglobin >100g/L.[30]

e) The maximum threshold hemoglobin to trigger RBC transfusion in the context of a study amongst the 531 intensivists, neurointensivists and neurosurgeons surveyed was 100g/L. [23]

Control: Restrictive RBC Transfusion Trigger (80g/L): Supported by:

a) In a survey of 531 practicing intensivists, neurointensivists and neurosurgeons in North America the median hemoglobin to trigger a transfusion ranged from 75 to 80g/L depending on SAH grade. [23]

b) Amongst practicing intensivists, neurointensivists and neurosurgeons the lowest acceptable threshold hemoglobin to trigger a RBC transfusion was 70g/L in >70% of respondents. [23]

c) A Canadian multi-center observational study (N=434) conducted in 4 academic centers in 2012 and 2013 completed by the SAHaRA study team demonstrated that the median pre-transfusion hemoglobin was 79g/L (IQR 74-93g/L).[31]

A transfusion trigger of 100g/L has previously been shown to be safe in an aSAH population.[18] The allocated transfusion strategy will be applied from the time of randomization to day 21 after the original bleed, death or hospital discharge, whichever comes first. The first 21 days following aSAH represents the period of greatest vulnerability to the direct consequences of aSAH, and the sequelae, including vasospasm, that follow.

Outcomes

Primary outcome

The primary feasibility endpoint is the number of patients randomized per center per month over the study period. We expect, amongst patients suffering from aSAH and anemia, 1.5 patients/month at each of 5 sites to be randomized into the trial. We reason that an optimal randomization rate of 1.5 participants/month/site and as low as 1 participant/month/site, will be necessary to demonstrate the feasibility of conducting the larger planned trial (Figure 2). This

outcome is objective, readily measurable, and feasible based on data generated from a cohort study conducted by the authors.

Secondary outcomes

a) *Transfusion threshold adherence* will be described as the proportion of "per protocol" RBC transfusion *events*. A transfusion threshold event is defined as an occurrence which starts when a hemoglobin value is measured at or below the allocated threshold for the first time since the previous event and ends when one of the following occurs: 1) an RBC transfusion is administered; or 2) a repeat hemoglobin is obtained above the allocated threshold within 24 hours of the original measure.

Transfusion threshold **non-adherence** will be considered to have occurred with any of the following: 1) an RBC transfusion occurs before a transfusion threshold is crossed; or 2) in the liberal arm, a transfusion is not given following a threshold crossing. Transfusion threshold non-adherence will be considered a *deviation* if: 1) the early transfusion occurs within 5 g/L above the allocated threshold (eg: ≤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 (ie: a transfusion does not occur for a Hb of 95-100 g/L). All other threshold event non-adherences that are greater or less than 5 g/L for the liberal threshold and greater than 5 g/L below the restrictive threshold will be considered a protocol violation. Transfusion outside of hemoglobin thresholds for symptomatic anemia or in the event of an active blood loss associated with hemodynamic instability, as defined by the treating team, will be recorded, but not considered a protocol violation. Details on non-adherence (date and hemoglobin level prior to transfusion) and reasons for non-adherence (e.g. physician preference, patient instability, active bleeding, safety concern) will be recorded.

b) *RBC transfusion protocol adherence:* The SAHaRA investigators recognize the importance of minimizing exposure time below the allocated transfusion threshold and thus every effort shall be put forth to administer the transfusion expeditiously. For the pilot we endeavor not to exceed 6 hours from transfusion threshold event to transfusion initiation, in keeping with revascularization time performance measures in stroke literature.[32,33] Median time (and interquartile range) to RBC transfusion will be described. Transfusion protocol adherence will be defined as the proportion of RBC transfusions that are initiated within 6 hours. 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 between 6 and 24 hours will be considered a protocol deviation and greater than 24 hours from the threshold event will be considered a violation.

c) *Clinical outcome ascertainment* will include ability to capture vital status at discharge, modified Rankin Scale (mRS) score at 6 and 12 months and the Functional Independence Measure (FIM) and the EuroQOL Quality of Life Scale (EQ5D) at 12 months. The mRS, FIM and EQ5D will be completed by assessors blinded to participant treatment allocation. Each of the outcome assessment measures have been selected because they examine different aspects of the 3 primary levels of body function and stroke rehabilitation (impairment, activity and participation)[34] and are specifically validated and recommended outcome measures in stroke research.[35] The mRS is used as the outcome measure over mortality as it includes a spectrum allowing consideration of severe disability and mortality together as both are highly clinically significant. Neurologic outcome as assessed by mRS is a common outcome in the aneurysmal SAH literature[9,18,36–39] and is readily interpretable in this community. It takes <15 minutes to administer, and can be completed using a structured interview[40–42] or as a telephone

interview.[43] The FIM is a validated[44,45] tool consisting of 18 items that assesses 13 different motor and 5 cognitive tasks previously tested in stroke populations including aSAH,[44,46] and has an established minimal clinical important difference (MCID) in this population.[47] 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.[34] The EQ5D is a short and simple 2-part questionnaire that may be self-administered, completed by interview or via a proxy respondent, and is used to value and describe health states.[34]

Baseline Characteristics, Co-Intervention, Outcome Assessment and Follow-up:

A secure web-based pre-piloted data collection form will be maintained by the host center and utilized for data entry and management. Important baseline characteristics (Table 1A) will be captured at time of enrolment for comparison between the 2 study groups to demonstrate the effectiveness of randomization. In this trial, patient management outside of RBC transfusion will be left to the discretion of the treating team and in accordance with practice guidelines[19] which will be made available to all participating centers and clinicians. All major co-interventions (eg: vasospasm, aneurysm and blood pressure management - Table 1B) will be carefully documented with daily record by the investigative team. Other clinical outcomes being collected include incidence and severity of vasospasm, incidence of cerebral infarction not directly related to complication from securing aneurysm, need for intubation, tracheostomy, percutaneous gastrostomy tube and/or ventricular shunt and ICU and hospital lengths of stay.

Table 1: Important baseline characteristics and co-interventions to be prospectively collected

A: Baseline characteristics (from time of enrolment and randomization)

Factor	Variable to capture
Age at enrolment[7,14,24,48,49]	Age in years
Sex[6]	Male or Female

History of CAD, HTN[6,49]	Present or not
SAH Clinical Severity [6,7,13,14,24,48,49]	WFNS score
SAH radiographic Severity[13,24,49]	Modified Fisher Scale Score
Hydrocephalus[49]	Need for EVD
Aneurysm size and location[48]	Size (mm), artery involved
Method aneurysm secured[6,24,50]	Clip or coil or not secured
Presence of vasospasm[7,10,13,24,49]	Radiographic or clinical vasospasm*
Presence of cerebral infarct[5,48,49]	Cerebral infarct on pre-randomization imaging

CAD=coronary artery disease, EVD=external ventricular drain, HTN=hypertension, SAH=subarachnoid hemorrhage, WFNS=World Federation of Neurosurgeons, *radiographic vasospasm defined as a reduction of cerebral artery diameter on digital subtraction angiography and classified as mild (0-33% reduction), moderate (34-66% reduction) or severe (67-100% reduction) or by transcranial Doppler with a mean middle or anterior cerebral artery flow velocity of >200cm/s or an increase of >50cm/s/24h on repeated measures and a Lindegaard ratio of ≥3, clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of ≥2 points for ≥2 hours or new focal neurological deficit)

B: Co-Interventions

Co-Intervention		Variable to capture	Operationalization
Vasospasm*[7,10,13,48,49]	Vasospasm prophylaxis	Hyperdynamic therapy (prior to diagnosis of vasospasm)	-use of vasopressors to drive a target MAP>65mmHg
			-use of IV fluid infusions or regular boluses over maintenance
			-use of IV fluids to target specific hematocrit
		Magnesium (prior to diagnosis of vasospasm)	-use of magnesium IV infusion
		Chemical vasodilators (prior to diagnosis of vasospasm)	-use of infusion of vasodilator (IV) or any IA use (eg: milrinone, paperavine, CCB etc)
	Vasospasm treatment	Hyperdynamic therapy (after diagnosis of vasospasm)	-same criteria as above
		Magnesium	-same criteria as above
		Mechanical vasodilation	-use of balloon angioplasty
		Chemical vasodilation	-use of infusion of vasodilator (IV) or any IA use (eg: milrinone, paperavine, CCB etc).
Definitive Aneurysm Management (if completed post randomization)[6,24]		Clip vs coil	-used or not
		Time to clip or coil	-minutes
Blood pressure management[31]		-daily use of vasopressor	-used or not
		-highest daily target MAP	-mmHg
Fever/temperature regulation[5,48]		-fever	-daily highest temperature

MAP=mean arterial pressure, IV=intravenous, IA=intra-arterial, CCB=calcium channel blocker, *radiographic vasospasm defined as a reduction of cerebral artery diameter on digital subtraction angiography and classified as mild (0-33% reduction),

moderate (34-66% reduction) or severe (67-100% reduction) or by transcranial Doppler with a mean middle or anterior cerebral artery flow velocity of >200cm/s or an increase of >50cm/s/24h on repeated measures and a Lindegaard ratio of ≥3, clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of ≥2 points for ≥2 hours or new focal neurological deficit)

Descriptive metrics will be used to measure feasibility including the primary outcome of randomization rate. These data will be gathered prospectively at each study center by a trained and qualified study nurse or practitioner using an electronic case report form. The number of eligible but not enrolled patients will be tracked, and reasons for non-enrollment will be recorded. Protocol adherence will be assessed prospectively by trained study personnel and all episodes of non-adherence to protocol will be adjudicated by 3 members of the steering committee, blinded to clinical outcome. Protocol adherence will be reported as a ratio of total correct transfusion threshold events to a combination of total number of transfusion events (needed or not needed per protocol) and total number of missed transfusion non-adherence events. Feasibility of outcome assessment will be measured by the ability to obtain the defined outcome measures at the pre-specified time periods. The three outcome measurement instruments (mRS, FIM and EQ5D) will be implemented by a trained and qualified study coordinator blinded to the intervention according the defined schedule (Table 2). Vital status at discharge and adverse events will be captured using a case report form prospectively by the site investigator or the research coordinator.

Table 2: Schedule of assessments

Assessment:	Baseline:	Prospective – Daily	Hospital Discharge	6 months	12 months
Eligibility Criteria	X				
Recruitment	X				
Informed Consent	X				
Randomization	X				
Baseline Demographics	X				
Medical History	X				
Physical Exam including BP, O_2 sat, GCS	X	X	X		

Baseline labs	X				
aSAH clinical grade	X				
Neuro imaging (U/S, CT, MRI, Angio...)	X				
Vasospasm monitoring (CTA, U/S, angio...) and management	X	X	X		
Laboratory results		X	X		
Transfusion Requirements		X	X		
Co-intervention Log		X	X		
Adherence to treatment		X	X		
AE Review		X	X		
Neurologic outcome (mRS)			X	X	X
Functional Independence Measure (FIM)					X
EuroQOL Quality of Life Scale (EQ5D)					X

GCS: Glasgow Coma Score; U/S: ultrasound.

Executive and Steering Committee Roles and Responsibilities

The Ottawa Hospital Research Institute is the host and trial method's center. The eight members of the SAHaRA Executive Committee will oversee all aspects of the study as well as larger research agenda business and will meet quarterly (via teleconference) to discuss any challenges. The Executive Committee will also contribute to the formulation of the analytical plan, data interpretation, and the drafting and revisions of future manuscripts. The Steering Committee will consist of all co-investigators participating in the trial. They are responsible for all aspects of study initiation and conduct at their respective sites. These include timely submissions to research ethics boards and supervision of the research coordinators who will screen, enroll, consent and collect data during the pilot, monitoring of recruitment and monitoring adherence to study protocol, and any operational challenges associated with the pilot RCT.

Ethics, Confidentiality and Data Monitoring Body

The study protocol has been approved by the host center (Ottawa Health Science Network Research Ethics Board (REB) - OHSN-REB 20150433-01H). The **intervention and control** arm of the trial are part of usual care in many centers, and thus the research risk to participants is minimal. Safety considerations are addressed within the protocol, and allow for individualized care where needed. In addition to potentially intervention-related adverse event reporting, pre-defined expected adverse events will be prospectively monitored and include acute respiratory distress syndrome, cardiovascular failure, cardiac ischemia/infarction, venous thromboembolic events, septic shock, hospital acquired infections and transfusion reactions.

All participant data will be de-identified to ensure confidentiality and through the assignment of an anonymous identifier by the web-based randomization tool and data collection form. All data will be collected and stored in firewall-protected, secure servers at the host center according to institutional and REB policy and in accordance with Good Clinical Practice.

A three-member independent Data Safety Monitoring Committee (DSMC) has been assembled and will oversee the progression of ascertaining the pilot objectives and all trial safety aspects according to a prescribed schedule, DSMC Charter and GCP reporting.

Sample Size

A sample size of 60 patients will allow us to evaluate enrolment rate averaging 1.5 patients per month per center with 5 centers over a 1-year study period. Based on our cohort study, we expect that 90 eligible patients will need to be screened into the study to achieve a randomized sample of 60 patients (that is more than 2/3 of patients with a hemoglobin of ≤110g/L had a nadir of 100g/L or less). All 5 proposed pilot trial sites are academic tertiary care centres with approximately 60-120 aSAH admissions per year. Our sample size will also allow the

demonstration of a protocol adherence rate of 90% with a 95% confidence interval of 82.4% to 97.6%.

Analytical Plan

a) **Descriptive Analyses:** Baseline characteristics and management data will be presented with means (continuous measures) or proportions (categorical or ordinal data) with 95% confidence intervals.

b) **Primary Outcome:** Using descriptive statistics, the median randomization rate (patients/month) overall and per center over the study duration will be calculated and reported with interquartile range. Only actual months where each center is actively recruiting patients will be considered in the analysis (i.e.: staggered start up across centers). Figure 2 demonstrates the effect of different randomization rates on study duration and hence feasibility. A rate of <1 patients/month per center will prompt a site review of the screening log to examine reasons for missed eligible patients and to discuss how to increase recruitment rate. Achieving our internal pilot primary objective of a randomization rate of 1.5 patients per month per center will allow us to complete the large trial in 3.5 years with 10 recruiting centers.

c) **Secondary Outcomes:** Secondary feasibility outcomes will be reported using descriptive statistics. Protocol adherence will be reported as a proportion as described above. Overall protocol adherence as well as adherence in the 2 individual study arms will be reported. Given the internal pilot design, with the plan to include these data in the large trial if no substantial changes to the protocol are made after the pilot trial, clinical outcomes will be described in aggregate using descriptive statistics.

Study Timeline

We estimate a study duration of 30 months. Study center identification is complete. Patient enrolment began in mid-October 2015 and will take 12 months per center to complete or 16 months total assuming a staggered start (to allow for different lead times for site preparation including contracts and REB approval). The last clinical outcome measure is thus expected at 28 months leaving 2 additional months for data cleaning and analysis for manuscript preparation.

Dissemination

The results of the SAHaRA Pilot RCT will be disseminated to the participating centers. As an internal pilot RCT, should no significant modification of the protocol be necessary, participant data will be included in the planned larger trial powered to clinically important outcomes. The results of the pilot will be incorporated with the larger trial and submitted to peer-reviewed journals for publication and presented at conferences.

DISCUSSION

The TRICC trial,[22] the first rigorous trial comparing different red blood cell transfusion thresholds in a critically ill patient population, remains significant today and continues to guide management of many ICU populations. However, several sub-populations were underrepresented (or not at all) in this study, such that the debate of optimal transfusion threshold continues to plague physicians at certain ICU bedsides. The neurocritically ill, specifically aneurysmal subarachnoid hemorrhage patients are such a population. The clinical importance of varied transfusion thresholds in aSAH has never been studied in a large and rigorous randomized trial. The only RCT used transfusion thresholds that differ significantly from stated current practice, and was not powered for clinically meaningful outcomes.[18] The need for quality evidence to guide transfusion practice in aSAH has been identified by many influential societies,

editorials and practice guidelines.[15,19,20,51] The uncritical use of variable thresholds does not advance patient outcome or physician practice.

Accomplishing the feasibility objectives of this pilot trial will ensure the successful completion of the future large trial. A pilot trial powered to feasibility outcomes is the essential initial step in the preparation for and eventual successful completion of the more costly larger trial, powered to clinically relevant outcomes.[52] Our multi-center design is essential to demonstrate feasibility of enrollment and randomization into the study and across centers. A 12-month enrollment period will enable us to determine the feasibility of recruitment at individual centers. Only an open label design is feasible in a RBC transfusion strategy trial given the inability to blind bedside clinicians to hemoglobin levels in the safe management of these patients. Similar open label trial designs have been successfully completed in RBC transfusion trials involving other patient populations.[22,53–55] Further, prospective randomized open-label blinded end-point (PROBE) designs have been used in multiple successful, practice-changing stroke trials.[56–58] To minimize potential bias imposed from open label treatments, our clinical outcome measures will be completed by a blinded assessor who has not been involved in patient management and is unaware of treatment assignment. We will demonstrate the feasibility of collecting the proposed clinical outcomes of the large RCT (neurologic functional outcome using mRS at 6 months and 1 year, as well as the FIM and EQ5D at 1 year) by observing the same follow-up schedule.

The results of the SAHaRA internal pilot trial will directly inform the conduct of and guide the successful completion of the larger RCT. The SAHaRA trial will clarify the role of treating anemia with RBC transfusion in this unique and vulnerable patient population, and whether that

impacts on functional outcome and mortality. We hypothesize an improvement in outcome with the treatment of anemia which, if substantiated, would dramatically change the management of these patients by intensivists, neurologists and neurosurgeons world-wide. A null result would provide the necessary evidence to the bedside clinician that a restrictive transfusion approach is safe and prevent the unnecessary risk imposed by blood product transfusion that regularly occurs.

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AUTHORS CONTRIBUTIONS

SE, LM, DAF, MC and AFT conceived the project idea. SE, LM, DAF, MC, AFT, LF, DG, AA, AHK, AT, CL, JS, SM, DD, AB, and GP all contributed substantially to the design of the trial and drafting of the protocol. SE created the first draft of this submission and all authors have provided critical review and approve of this final version.

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COMPETING INTERESTS

None.

FIGURE LEGEND

Figure 1: SAHaRA Trial Design

Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation of enrollment

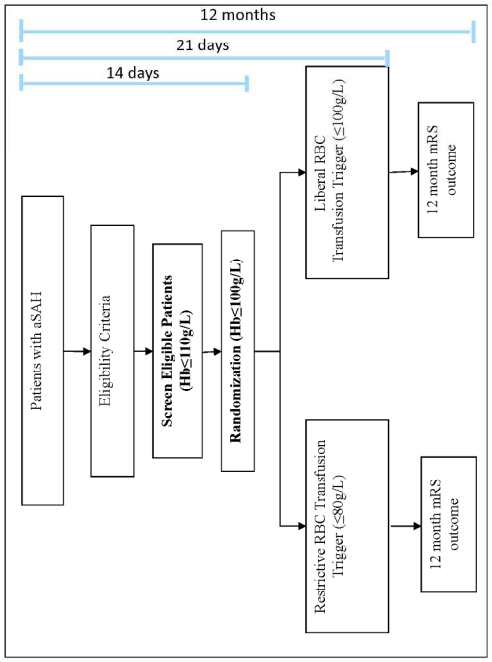

Figure 1: SAHaRA Trial Design
Figure 1
215x279mm (300 x 300 DPI)

Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation of enrollment
Figure 2
215x279mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on line number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____4-5____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____50, 78_____
	2b	All items from the World Health Organization Trial Registration Data Set	__as below_____
Protocol version	3	Date and version identifier	_____n/a_____
Funding	4	Sources and types of financial, material, and other support	__45-48, 618-621_
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__14-33, 613-317_
	5b	Name and contact information for the trial sponsor	_____n/a_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____n/a_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___343-353___

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___88-122___
	6b	Explanation for choice of comparators	__111-119____
Objectives	7	Specific objectives or hypotheses	_119-121,131-137
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____115, 125-130
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____128_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__142-158___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__192-207____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___265-268_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___243-301_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___306-308____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__241-301_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__347, 624_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___377-385_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___169-179____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_183-185, 187-191
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_183-185, 188-191
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_180-191_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	129-130,285,444-446
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__302-330_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___282-301____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	303-304,370-373,333-338
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_377-405_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__n/a_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__n/a_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__374-376_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___n/a_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__365-369_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__n/a_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__362-63,180-183
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__n/a_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	180-183, 358-360
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_n/a_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	185-187,332-334,370-373_
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_609-611,622____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_n/a_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__412-417_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____n/a_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n/a___
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____n/a_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.