

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-012623
Article Type:	Protocol
Date Submitted by the Author:	12-May-2016
Complete List of Authors:	English, Shane; University of Ottawa, Medicine (Critical Care); Ottawa Hospital Research Institute, Clinical Epidemiology Program Fergusson, Dean; Ottawa Hospital Research Institute, Surgery Chassé, Michaël; CHU de Quebec, Anesthesiology and Critical Care Turgeon, Alexis; Centre de Recherche du Centre Hospitalier Affilié Universitaire de Québec (CHA), Axe Traumatologie-urgence-soins intensifs, CHA-Hôpital de l'Enfant-Jésus, Université Laval, Anesthesia and Critical Care Medicine Lauzier, Francois Griesdale, Donald; University of British Columbia Algird, Almunder; Hamilton Health Sciences, Neurosurgery Kramer, Andreas H.; Univ Calgary Tinmouth, Alan; Ottawa Hospital Research Institute, Clinical Epidemiology Lum, Cheemun; The Ottawa Hospital, Radiology Sinclair, John; The Ottawa Hospital, Neurosurgery Marshall, Shawn; The Ottawa Hospital, Rehabilitation and Physiatry Dowlatshahi, Dariush; The Ottawa Hospital, Neurology Boutin, A; Université Laval Pagliarello, Giuseppe; The Ottawa Hospital, Surgery McIntyre, Lauralyn; Ottawa Hospital Research Institute, Clinical Epidemiology
<b>Primary Subject Heading</b>:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Intensive care
Keywords:	Anaemia < HAEMATOLOGY, Blood bank & transfusion medicine < HAEMATOLOGY, Stroke < NEUROLOGY, NEUROSURGERY, Clinical trials < THERAPEUTICS

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 **Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome**  
12 **(SAHaRA): A Pilot Randomized Controlled Trial Protocol**  
13  
14  
15  
16  
17  
18  
19

20 Shane W English<sup>1,2</sup>, D Fergusson<sup>2</sup>, M Chassé<sup>3,4</sup>, AF Turgeon<sup>3,4</sup>, F Lauzier<sup>3,4</sup>, D Griesdale<sup>5</sup>, A  
21 Algird<sup>6</sup>, A Kramer<sup>7,8</sup>, A Tinmouth<sup>2</sup>, C Lum<sup>2</sup>, J Sinclair<sup>2</sup>, S Marshall<sup>2</sup>, D Dowlatshahi<sup>1,2</sup>, A  
22 Boutin<sup>4</sup>, G Pagliarello<sup>2</sup>, and L McIntyre<sup>1,2</sup>, on behalf of the Canadian Critical Care Trials Group.  
23  
24  
25  
26  
27  
28  
29  
30  
31

32 **Affiliation:**

33  
34 <sup>1</sup>Department of Medicine, University of Ottawa, Ottawa Canada

35  
36 <sup>2</sup>Clinical Epidemiology Program (Centre for Transfusion Research), Ottawa Hospital Research  
37 Institute, Ottawa Canada  
38

39  
40 <sup>3</sup>Department of Anesthesiology & Critical Care, Division of Critical Care Medicine, Université  
41 Laval, Québec City, Canada  
42

43  
44 <sup>4</sup>CHU de Québec - Université Laval Research Center, Population Health and Optimal Health  
45 Practices Unit (Trauma - Emergency - Critical Care Medicine), Québec City, Canada  
46

47  
48 <sup>5</sup>Department of Anesthesiology, Pharmacology and Therapeutics, University of British  
49 Columbia, Vancouver, Canada  
50

51  
52 <sup>6</sup>Department of Surgery (Neurosurgery), McMaster University, Hamilton, Canada  
53  
54  
55  
56  
57  
58  
59  
60

<sup>7</sup>Department of Critical Care, University of Calgary, Calgary, Canada

<sup>8</sup>Department of Clinical Neurosciences and the Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

### Correspondence:

Shane English

Department of Medicine (Critical Care), The Ottawa Hospital

Civic Campus Room F202

1053 Carling Avenue

Ottawa ON K1Y 4E9

Canada

613-737-8899 ext. 72818

senglish@ohri.ca

### Funding:

The SAHaRA Pilot Trial is funded by a Transfusion Science research grant awarded by a Canadian Blood Services and Health Canada in partnership with Canadian Institutes of Health Research (CIHR) Institute of Circulatory and Respiratory Health.

**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 ( $Hb \leq 100g/L$ ), comparing a liberal transfusion strategy ( $Hb \leq 100g/L$ ) to a restrictive strategy ( $Hb \leq 80g/L$ ) 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 ( $Hb \leq 110g/L$ ). **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  $\leq 100g/L$ . **Intervention:** Patients will be randomly assigned to either a liberal (threshold:  $Hb \leq 100g/L$ ) or a restrictive transfusion strategy (threshold:  $Hb \leq 80g/L$ ). **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

1  
2  
3 RCT comparing 2 RBC transfusion strategies examining the effect of a liberal strategy on 12-  
4  
5  
6 month outcome following aSAH. (Trial Registry No.: NCT 02483351)  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## 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

1  
2  
3 to substantiate these recommendations. Current stated and observed practice from surveys[23]  
4  
5 and our own observational work suggest a more restrictive approach to transfusion (lower  
6  
7 hemoglobin); similar to other critical care patients. However, unlike other critically ill patients,  
8  
9 brain injury and the sequelae that follow (e.g.: vasospasm and delayed cerebral ischemia) may  
10  
11 make these patients more susceptible to the decreased oxygen delivery associated with a lower  
12  
13 transfusion threshold. Considering this obvious paradox and confliction, there is pressing need to  
14  
15 generate high-quality evidence to guide clinical RBC transfusion practices in aSAH. The clinical  
16  
17 impact of varied transfusion thresholds in aSAH has never been studied in a large and rigorous  
18  
19 randomized trial. In collaboration with the Canadian Critical Care Trials Group ([www.ccctg.ca](http://www.ccctg.ca)),  
20  
21 we aim to conduct such an RCT comparing two RBC transfusion strategies in adult patients with  
22  
23 aSAH powered for clinically relevant outcomes. To inform and justify our large trial, we are  
24  
25 conducting a pilot RCT to assess feasibility and strengthen the design of the large-scale trial.  
26  
27  
28  
29  
30  
31  
32  
33

## 34 **METHODS AND ANALYSIS**

### 36 **Study Design**

37  
38 The Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome: A  
39  
40 Pilot Randomized Controlled Trial (SAHaRA Pilot Trial) is a Canadian multicenter (5) open-  
41  
42 label randomized controlled pilot trial in patients with an acute aSAH. To reduce bias from the  
43  
44 open-label design, outcome assessors will be blinded to the treatment assignments.  
45  
46  
47

### 48 **Patient Population**

49  
50 To facilitate randomization into the pilot trial, a subset of patients most likely to meet  
51  
52 randomization criteria will be identified (Screen Eligible Patients). To be screened eligible for  
53  
54 enrolment, patients must meet all inclusion criteria and no exclusion criteria.  
55  
56  
57  
58  
59  
60

1  
2  
3 Inclusion Criteria:  
4

- 5  
6 1. Age  $\geq 18$  years old at time of presentation  
7  
8 2. First ever episode aSAH  
9  
10 3. Confirmed aSAH diagnosis: as confirmed by treating neurosurgeon or neuro-  
11 interventionalist and supported by blood in subarachnoid space (demonstrated on cranial  
12 imaging or cerebrospinal fluid positive for xanthochromia) that is the result of a ruptured  
13 saccular aneurysm (confirmed by cranial imaging – computed tomography, magnetic  
14 resonance or catheter angiogram)  
15  
16 4. Incident Hb  $\leq 110$ g/L within 14 days following aSAH (defined by first day of hospital  
17 presentation)  
18  
19  
20  
21  
22  
23  
24  
25  
26

27 Exclusion Criteria:  
28

- 29 1. Physician and or next of kin decision to withdraw/withhold critical care at time of  
30 enrolment  
31  
32 2. Active bleeding with hemodynamic instability at time of enrolment  
33  
34 3. Patients with contraindication or known objection to blood transfusions  
35  
36 4. SAH due to causes other than saccular aneurysm rupture including mycotic, traumatic  
37 and dissecting aneurysms, and aneurysms associated with arteriovenous malformations  
38  
39  
40  
41  
42

43 Our exclusion criteria are in place to prevent enrolling patients who: 1) would not benefit from  
44 the intervention; 2) object to the intervention; and/or 3) have sustained a bleed due to  
45 mechanistically different causes whose pathophysiological properties are not necessarily shared  
46 with aSAH.  
47  
48  
49  
50  
51

52 Screen eligible patients who experience an incident Hb  $\leq 100$  g/L within 14 days  
53 following aSAH will be randomized.  
54  
55  
56  
57  
58  
59  
60



### 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

1  
2  
3 web interface. Upon meeting the randomization criteria, patients will be randomized in a 1:1  
4  
5 manner to either liberal (intervention) or restrictive (control) RBC transfusion strategy groups. A  
6  
7 schedule of the random treatment allocations, stratified by center will be prepared by an  
8  
9 independent biostatistician at the Coordinating Center. All investigative team members will  
10  
11 remain blinded to the allocation schedules.  
12  
13

### 14 15 **Intervention**

16  
17 Patients fulfilling the eligibility criteria will be randomized to either a liberal or restrictive RBC  
18  
19 transfusion strategy.  
20  
21

#### 22 *Intervention Group: Liberal RBC Transfusion Strategy:*

23  
24 In this intervention group, an RBC transfusion will be triggered by a hemoglobin level of  
25  
26  $\leq 100\text{g/L}$  over the first 21 days in hospital following aSAH.  
27  
28

#### 29 *Control Group: Restrictive RBC Transfusion Strategy*

30  
31 For patients randomized to this group, an RBC transfusion is permitted once a hemoglobin level  
32  
33 of  $\leq 80\text{g/L}$  is observed over the first 21 days in hospital following aSAH. RBC transfusion will  
34  
35 not be mandatory under this threshold, “usual care” rather will prevail, and the decision to and  
36  
37 timing of transfusion will be left to the discretion of the treating team.  
38  
39

#### 40 41 *Both Groups*

42  
43 All RBC transfusions will be a single unit unless the patient has an active blood loss associated  
44  
45 with hemodynamic instability. In stable non-bleeding patients, a second unit of RBCs should  
46  
47 only be given if a measured post-transfusion hemoglobin level remains below the patient’s  
48  
49 assigned threshold.  
50  
51

#### 52 53 *Justification of the two triggers*

54  
55 Intervention: Liberal RBC Transfusion Trigger (100g/L): Supported by:  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38
- 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]

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

- 40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 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]

- 1  
2  
3 c) A Canadian multi-center observational study (N=434) conducted in 4 academic centers in  
4  
5 2012 and 2013 completed by the SAHaRA study team demonstrated that the median pre-  
6  
7 transfusion hemoglobin was 79g/L (IQR 74-93g/L).[31]  
8  
9

10 A transfusion trigger of 100g/L has previously been shown to be safe in an aSAH  
11  
12 population.[18] The allocated transfusion strategy will be applied from the time of randomization  
13  
14 to day 21 after the original bleed, death or hospital discharge, whichever comes first. The first 21  
15  
16 days following aSAH represents the period of greatest vulnerability to the direct consequences of  
17  
18 aSAH, and the sequelae, including vasospasm, that follow.  
19  
20  
21  
22  
23

## 24 **Outcomes**

### 25 *Primary outcome*

26  
27 The primary feasibility endpoint is the number of patients randomized per center per month over  
28  
29 the study period. We expect, amongst patients suffering from aSAH and anemia, 1.5  
30  
31 patients/month at each of 5 sites to be randomized into the trial. We reason that an optimal  
32  
33 randomization rate of 1.5 participants/month/site and as low as 1 participant/month/site, will be  
34  
35 necessary to demonstrate the feasibility of conducting the larger planned trial (Figure 2). This  
36  
37 outcome is objective, readily measurable, and feasible based on data generated from a cohort  
38  
39 study conducted by the authors.  
40  
41  
42  
43  
44

### 45 *Secondary outcomes*

46  
47 a) *Transfusion threshold adherence* will be described as the proportion of “per protocol” RBC  
48  
49 transfusion *events*. A transfusion threshold event is defined as an occurrence which starts when a  
50  
51 hemoglobin value is measured at or below the allocated threshold for the first time since the  
52  
53 previous event and ends when one of the following occurs: 1) an RBC transfusion is  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 administered; or 2) a repeat hemoglobin is obtained above the allocated threshold within 24  
4  
5 hours of the original measure.  
6  
7

8 Transfusion threshold **non-adherence** will be considered to have occurred with any of the  
9  
10 following: 1) an RBC transfusion occurs before a transfusion threshold is crossed; or 2) in the  
11  
12 liberal arm, a transfusion is not given following a threshold crossing. Transfusion threshold non-  
13  
14 adherence will be considered a *deviation* if: 1) the early transfusion occurs within 5 g/L above  
15  
16 the allocated threshold (eg:  $\leq 105$  g/L for the liberal arm or  $\leq 85$  g/L for the restrictive arm) or, 2)  
17  
18 in the liberal arm, an RBC transfusion does not occur for a hemoglobin measure up to 5 g/L  
19  
20 below the threshold (ie: a transfusion does not occur for a Hb of 95-100 g/L). All other threshold  
21  
22 event non-adherences that are greater or less than 5 g/L for the liberal threshold and greater than  
23  
24 5 g/L below the restrictive threshold will be considered a protocol violation. Transfusion outside  
25  
26 of hemoglobin thresholds for symptomatic anemia or in the event of an active blood loss  
27  
28 associated with hemodynamic instability, as defined by the treating team, will be recorded, but  
29  
30 not considered a protocol violation. Details on non-adherence (date and hemoglobin level prior  
31  
32 to transfusion) and reasons for non-adherence (e.g. physician preference, patient instability,  
33  
34 active bleeding, safety concern) will be recorded.  
35  
36  
37  
38  
39

40  
41 b) *RBC transfusion protocol adherence*: The SAHaRA investigators recognize the importance of  
42  
43 minimizing exposure time below the allocated transfusion threshold and thus every effort shall  
44  
45 be put forth to administer the transfusion expeditiously. For the pilot we endeavor not to exceed  
46  
47 6 hours from transfusion threshold event to transfusion initiation, in keeping with  
48  
49 revascularization time performance measures in stroke literature.[32,33] Median time (and  
50  
51 interquartile range) to RBC transfusion will be described. Transfusion protocol adherence will be  
52  
53 defined as the proportion of RBC transfusions that are initiated within 6 hours. Non-adherence  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 will be considered to have occurred if there is a delay of more than six hours between transfusion  
4 threshold event and transfusion initiation. Transfusions occurring between 6 and 24 hours will be  
5 considered a protocol deviation and greater than 24 hours from the threshold event will be  
6 considered a violation.  
7  
8  
9  
10  
11

12 c) *Clinical outcome ascertainment* will include ability to capture vital status at discharge,  
13 modified Rankin Scale (mRS) score at 6 and 12 months and the Functional Independence  
14 Measure (FIM) and the EuroQOL Quality of Life Scale (EQ5D) at 12 months. The mRS, FIM  
15 and EQ5D will be completed by assessors blinded to participant treatment allocation. Each of  
16 the outcome assessment measures have been selected because they examine different aspects of  
17 the 3 primary levels of body function and stroke rehabilitation (impairment, activity and  
18 participation)[34] and are specifically validated and recommended outcome measures in stroke  
19 research.[35] The mRS is used as the outcome measure over mortality as it includes a spectrum  
20 allowing consideration of severe disability and mortality together as both are highly clinically  
21 significant. Neurologic outcome as assessed by mRS is a common outcome in the aneurysmal  
22 SAH literature[9,18,36–39] and is readily interpretable in this community. It takes <15 minutes  
23 to administer, and can be completed using a structured interview[40–42] or as a telephone  
24 interview.[43] The FIM is a validated[44,45] tool consisting of 18 items that assesses 13  
25 different motor and 5 cognitive tasks previously tested in stroke populations including  
26 aSAH,[44,46] and has an established minimal clinical important difference (MCID) in this  
27 population.[47] It has demonstrated excellent consistency in inter-rater reliability and internal  
28 consistency specifically in neurologic disorder populations. It is easy to administer and is  
29 validated for use by telephone and via proxy respondents.[34] The EQ5D is a short and simple 2-  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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)**

<b>Factor</b>	<b>Variable to capture</b>
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  $\geq 3$ , clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of  $\geq 2$  points for  $\geq 2$  hours or new focal neurological deficit)

**B: Co-Interventions**

	<u>Co-Intervention</u>	<u>Variable to capture</u>	<u>Operationalization</u>
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 <sup>31</sup>	-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  $\geq 3$ , clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of  $\geq 2$  points for  $\geq 2$  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**

<b>Assessment:</b>	<b>Baseline:</b>	<b>Prospective – Daily</b>	<b>Hospital Discharge</b>	<b>6 months</b>	<b>12 months</b>
<b>Eligibility Criteria</b>	X				
<b>Recruitment</b>	X				
<b>Informed Consent</b>	X				
<b>Randomization</b>	X				
<b>Baseline Demographics</b>	X				
<b>Medical History</b>	X				
<b>Physical Exam including BP, O<sub>2</sub> sat, GCS</b>	X	X	X		
<b>Baseline labs</b>	X				
<b>aSAH clinical grade</b>	X				
<b>Neuro imaging (U/S, CT, MRI, Angio...)</b>	X				
<b>Vasospasm monitoring (CTA, U/S, angio...) and management</b>	X	X	X		
<b>Laboratory results</b>		X	X		
<b>Transfusion Requirements</b>		X	X		
<b>Co-intervention Log</b>		X	X		
<b>Adherence to treatment</b>		X	X		
<b>AE Review</b>		X	X		
<b>Neurologic outcome (mRS)</b>			X	X	X

<b>Functional Independence Measure (FIM)</b>					X
<b>EuroQOL Quality of Life Scale (EQ5D)</b>					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.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40

**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.

41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

**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

55  
56  
57  
58  
59  
60

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

1  
2  
3 The TRICC trial,[22] the first rigorous trial comparing different red blood cell transfusion  
4 thresholds in a critically ill patient population, remains significant today and continues to guide  
5 management of many ICU populations. However, several sub-populations were  
6 underrepresented (or not at all) in this study, such that the debate of optimal transfusion threshold  
7 continues to plague physicians at certain ICU bedsides. The neurocritically ill, specifically  
8 aneurysmal subarachnoid hemorrhage patients are such a population. The clinical importance of  
9 varied transfusion thresholds in aSAH has never been studied in a large and rigorous randomized  
10 trial. The only RCT used transfusion thresholds that differ significantly from stated current  
11 practice, and was not powered for clinically meaningful outcomes.[18] The need for quality  
12 evidence to guide transfusion practice in aSAH has been identified by many influential societies,  
13 editorials and practice guidelines.[15,19,20,51] The uncritical use of variable thresholds does not  
14 advance patient outcome or physician practice.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33

34 Accomplishing the feasibility objectives of this pilot trial will ensure the successful completion  
35 of the future large trial. Our multi-center design is essential to demonstrate feasibility of  
36 enrollment and randomization into the study and across centers. A 12-month enrollment period  
37 will enable us to determine the feasibility of recruitment at individual centers. Only an open label  
38 design is feasible in a RBC transfusion strategy trial given the inability to blind bedside  
39 clinicians to hemoglobin levels in the safe management of these patients. Similar open label trial  
40 designs have been successfully completed in RBC transfusion trials involving other patient  
41 populations.[22,52–54] Further, prospective randomized open-label blinded end-point (PROBE)  
42 designs have been used in multiple successful, practice-changing stroke trials.[55–57] We will  
43 demonstrate the feasibility of collecting the proposed clinical outcomes of the large RCT  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 (neurologic functional outcome using mRS at 6 months and 1 year, as well as the FIM and EQ5D  
4  
5  
6 at 1 year) by observing the same follow-up schedule.  
7  
8  
9

10 The results of the SAHaRA internal pilot trial will directly inform the conduct of and guide the  
11 successful completion of the larger RCT. The SAHaRA trial will clarify the role of treating  
12 anemia with RBC transfusion in this unique and vulnerable patient population, and whether that  
13 impacts on functional outcome and mortality. We hypothesize an improvement in outcome with  
14 the treatment of anemia which, if substantiated, would dramatically change the management of  
15 these patients by intensivists, neurologists and neurosurgeons world-wide. A null result would  
16 provide the necessary evidence to the bedside clinician that a restrictive transfusion approach is  
17 safe and prevent the unnecessary risk imposed by blood product transfusion that regularly  
18 occurs.  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34

## 35 REFERENCES

- 36  
37  
38 1 Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from  
39 subarachnoid hemorrhage. *Neurology* 1998;**50**:1413–8.  
40  
41  
42  
43 2 Reed SD, Blough DK, Meyer K, *et al.* Inpatient costs, length of stay, and mortality for  
44 cerebrovascular events in community hospitals. *Neurology* 2001;**57**:305–14.  
45  
46  
47  
48  
49 3 Nieuwkamp DJ, Setz LE, Algra A, *et al.* Changes in case fatality of aneurysmal  
50 subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis.  
51 *Lancet Neurol* 2009;**8**:635–42.  
52  
53  
54  
55  
56  
57 4 Le Roux PD. Anemia and transfusion after subarachnoid hemorrhage. *Neurocrit Care*  
58  
59  
60

- 1  
2  
3 2011;**15**:342–53.  
4  
5  
6  
7 5 Springer M V, Schmidt JM, Wartenberg KE, *et al.* Predictors of global cognitive  
8 impairment 1 year after subarachnoid hemorrhage. *Neurosurgery* 2009;**65**:1043–50;  
9 discussion 1050–1.  
10  
11  
12  
13  
14 6 Sampson TR, Dhar R, Diringner MN. Factors associated with the development of anemia  
15 after subarachnoid hemorrhage. *Neurocrit Care* 2010;**12**:4–9.  
16  
17  
18  
19  
20 7 Naidech AM, Drescher J, Ault ML, *et al.* Higher hemoglobin is associated with less  
21 cerebral infarction, poor outcome, and death after subarachnoid hemorrhage.  
22 *Neurosurgery* 2006;**59**:775–9.  
23  
24  
25  
26  
27  
28 8 Wartenberg KE, Mayer SA. Medical complications after subarachnoid hemorrhage: new  
29 strategies for prevention and management. *Curr Opin Crit Care* 2006;**12**:78–84.  
30  
31  
32  
33 9 Naidech AM, Jovanovic B, Wartenberg KE, *et al.* Higher hemoglobin is associated with  
34 improved outcome after subarachnoid hemorrhage. *Crit Care Med* 2007;**35**:2383–9.  
35  
36  
37  
38  
39 10 Kramer AH, Gurka MJ, Nathan B, *et al.* Complications associated with anemia and blood  
40 transfusion in patients with aneurysmal subarachnoid hemorrhage. *Crit Care Med*  
41 2008;**36**:2070–5.  
42  
43  
44  
45  
46  
47 11 Kramer AH, Zygun DA. Anemia and red blood cell transfusion in neurocritical care. *Crit*  
48 *Care* 2009;**13**:R89.  
49  
50  
51  
52  
53 12 Amin M, Fergusson D, Wilson K, *et al.* The societal unit cost of allogenic red blood cells  
54 and red blood cell transfusion in Canada. *Transfusion* 2004;**44**:1479–86.  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 13 Smith MJ, Le Roux PD, Elliott JP, *et al.* Blood transfusion and increased risk for vasospasm and poor outcome after subarachnoid hemorrhage. *J Neurosurg* 2004;**101**:1–7.
- 14 Broessner G, Lackner P, Hofer C, *et al.* Influence of red blood cell transfusion on mortality and long-term functional outcome in 292 patients with spontaneous subarachnoid hemorrhage. *Crit Care Med* 2009;**37**:1886–92.
- 15 Levine J, Kofke A, Cen L, *et al.* Red blood cell transfusion is associated with infection and extracerebral complications after subarachnoid hemorrhage. *Neurosurgery* 2010;**66**:312–8; discussion 318.
- 16 C. Taylor, K. Gough, J. Gross MS. Transfusion threshold for acute aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 2012;**24**:254–5.
- 17 E. Mauricio, M. Robinson, J. Dajac, O. Gajic EF. Anemia, transfusion thresholds and incidence of vasospasm and infarction among patients with aneurysmal subarachnoid hemorrhage. *Crit Care Med* 2010;**38**:A86.
- 18 Naidech AM, Shaibani A, Garg RK, *et al.* Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage. *Neurocrit Care* 2010;**13**:313–20.
- 19 Connolly ES, Rabinstein AA, Carhuapoma JR, *et al.* Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012;**43**:1711–37.
- 20 Diringier MN, Bleck TP, Claude Hemphill J, *et al.* Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society’s Multidisciplinary Consensus Conference. *Neurocrit Care* 2011;**15**:211–40.

- 1  
2  
3 21 Lacroix J, Hébert PC, Hutchison JS, *et al.* Transfusion strategies for patients in pediatric  
4 intensive care units. *N Engl J Med* 2007;**356**:1609–19.  
5  
6  
7  
8  
9 22 Hébert PC, Wells G, Blajchman MA, *et al.* A multicenter, randomized, controlled clinical  
10 trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care  
11 Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;**340**:409–17.  
12  
13  
14  
15  
16  
17 23 Kramer AH, Diringner MN, Suarez JI, *et al.* Red blood cell transfusion in patients with  
18 subarachnoid hemorrhage: a multidisciplinary North American survey. *Crit Care*  
19 2011;**15**:R30.  
20  
21  
22  
23  
24 24 Kramer AH, Zygun D a, Bleck TP, *et al.* Relationship between hemoglobin concentrations  
25 and outcomes across subgroups of patients with aneurysmal subarachnoid hemorrhage.  
26 *Neurocrit Care* 2009;**10**:157–65.  
27  
28  
29  
30  
31  
32  
33 25 English SW, Chasse M, Turgeon A, *et al.* Aneurysmal subarachnoid hemorrhage and  
34 anemia: a canadian multi-centre retrospective cohort study. *Crit Care* 2016;**20**:P337.  
35  
36  
37  
38  
39 26 Dhar R, Scalfani MT, Zazulia AR, *et al.* Comparison of induced hypertension, fluid bolus,  
40 and blood transfusion to augment cerebral oxygen delivery after subarachnoid  
41 hemorrhage. *J Neurosurg* 2012;**116**:648–56.  
42  
43  
44  
45  
46 27 Smith MJ, Stiefel MF, Magge S, *et al.* Packed red blood cell transfusion increases local  
47 cerebral oxygenation. *Crit Care Med* 2005;**33**:1104–8.  
48  
49  
50  
51  
52 28 Kurtz P, Helbok R, Claassen J, *et al.* Effect of packed red blood cell transfusion on  
53 cerebral oxygenation and metabolism after subarachnoid hemorrhage. *Crit Care*  
54 2010;**14**:P341.  
55  
56  
57  
58  
59  
60



- 1  
2  
3  
4 29 Dhar R, Zazulia AR, Videen TO, *et al.* Red blood cell transfusion increases cerebral  
5 oxygen delivery in anemic patients with subarachnoid hemorrhage. *Stroke* (00392499)  
6 2009;**40**:3039–44.  
7  
8  
9  
10  
11 30 Kurtz P, Schmidt JM, Claassen J, *et al.* Anemia is associated with metabolic distress and  
12 brain tissue hypoxia after subarachnoid hemorrhage. *Neurocrit Care* 2010;**13**:10–6.  
13  
14  
15  
16  
17 31 English SW, Chasse M, Turgeon A, *et al.* Red blood cell transfusion in aneurysmal  
18 subarachnoid hemorrhage – the Sahara cohort study. *Crit Care* 2016;**20**:P336.  
19  
20  
21  
22 32 Jauch EC, Saver JL, Adams HP, *et al.* Guidelines for the early management of patients  
23 with acute ischemic stroke: a guideline for healthcare professionals from the American  
24 Heart Association/American Stroke Association. *Stroke* 2013;**44**:870–947.  
25  
26  
27  
28  
29  
30 33 Lindsay M, Gubitz G, Bayley M, *et al.* Canadian Best Practice Recommendations for  
31 Stroke Care (Update 2010). Ottawa ON Canada: 2010.  
32  
33  
34  
35  
36 34 Salter K, Campbell N, Richardson M, *et al.* Outcome Measures in Stroke Rehabilitation.  
37 In: *Evidence Based Research in Stroke Rehabilitation*. 2013. 1–144.  
38  
39  
40  
41 42 Sullivan JE, Crouner BE, Kluding PM, *et al.* Outcome measures for individuals with  
43 stroke: process and recommendations from the American Physical Therapy Association  
44 neurology section task force. *Phys Ther* 2013;**93**:1383–96.  
45  
46  
47  
48  
49 50 Hop JW, Rinkel GJ, Algra A, *et al.* Case-fatality rates and functional outcome after  
51 subarachnoid hemorrhage: a systematic review. *Stroke* 1997;**28**:660–4.  
52  
53  
54  
55 56 Nieuwkamp DJ, De Gans K, Rinkel GJ, *et al.* Treatment and outcome of severe  
57 intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a  
58  
59  
60

- 1  
2  
3  
4 systematic review of the literature. *J Neurol* 2000;**247**:117–21.
- 5  
6  
7 38 Kirkpatrick PJ, Turner CL, Smith C, *et al.* Simvastatin in aneurysmal subarachnoid  
8 haemorrhage (STASH): a multicentre randomised phase 3 trial. *Lancet Neurol*  
9 2014;**13**:666–75.
- 10  
11  
12  
13  
14 39 Dorhout Mees SM, Algra A, Vandertop WP, *et al.* Magnesium for aneurysmal  
15 subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet*  
16 2012;**380**:44–9.
- 17  
18  
19  
20  
21  
22 40 Banks JL, Marotta C a. Outcomes validity and reliability of the modified Rankin scale:  
23 implications for stroke clinical trials: a literature review and synthesis. *Stroke*  
24 2007;**38**:1091–6.
- 25  
26  
27  
28  
29  
30 41 Wilson JTL, Hareendran A, Hendry A, *et al.* Reliability of the modified Rankin Scale  
31 across multiple raters: benefits of a structured interview. *Stroke* 2005;**36**:777–81.
- 32  
33  
34  
35  
36 42 Wilson JTL. Improving the Assessment of Outcomes in Stroke: Use of a Structured  
37 Interview to Assign Grades on the Modified Rankin Scale. *Stroke* 2002;**33**:2243–6.
- 38  
39  
40  
41 43 Savio K, Luca G, Pietra D, *et al.* Reliability of the modified Rankin Scale applied by  
42 telephone. 2013;**5**:6–7.
- 43  
44  
45  
46  
47 44 O’Dell MW, Watanabe TK, De Roos ST, *et al.* Functional outcome after inpatient  
48 rehabilitation in persons with subarachnoid hemorrhage. *Arch Phys Med Rehabil*  
49 2002;**83**:678–82.
- 50  
51  
52  
53  
54  
55 45 Linacre JM, Heinemann AW, Wright BD, *et al.* The structure and stability of the  
56 Functional Independence Measure. *Arch Phys Med Rehabil* 1994;**75**:127–32.
- 57  
58  
59  
60

- 1  
2  
3  
4 46 Dromerick AW, Edwards DF, Diringner MN. Sensitivity to changes in disability after  
5 stroke: a comparison of four scales useful in clinical trials. *J Rehabil Res Dev*;40:1–8.  
6  
7  
8  
9 47 Beninato M, Gill-Body KM, Salles S, *et al.* Determination of the minimal clinically  
10 important difference in the FIM instrument in patients with stroke. *Arch Phys Med*  
11 *Rehabil* 2006;87:32–9.  
12  
13  
14  
15  
16  
17 48 Wartenberg KE, Schmidt JM, Claassen J, *et al.* Impact of medical complications on  
18 outcome after subarachnoid hemorrhage. *Crit Care Med* 2006;34:617–23; quiz 624.  
19  
20  
21  
22 49 Rodriguez DR, Matamoros CS, Fernandez LC, *et al.* Factors associated with poor  
23 outcome for aneurysmal subarachnoid hemorrhage in a series of 334 patients. *Neurologia*  
24 2015;:1–7.  
25  
26  
27  
28  
29  
30 50 Molyneux AJ, Kerr RSC, Yu L, *et al.* International subarachnoid aneurysm trial (ISAT) of  
31 neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured  
32 intracranial aneurysms: a randomised comparison of effects on survival, dependency,  
33 seizures, rebleeding, subgroups, and . *Lancet* 2005;366:809–17.  
34  
35  
36  
37  
38  
39  
40 51 Geocadin RG, Bleck TP, Koroshetz WJ, *et al.* Research priorities in neurocritical care.  
41 *Neurocrit Care* 2012;16:35–41.  
42  
43  
44  
45  
46 52 Carson JL, Terrin ML, Noveck H, *et al.* Liberal or restrictive transfusion in high-risk  
47 patients after hip surgery. *N Engl J Med* 2011;365:2453–62.  
48  
49  
50  
51  
52 53 Carson JL, Brooks MM, Abbott JD, *et al.* Liberal versus restrictive transfusion thresholds  
53 for patients with symptomatic coronary artery disease. *Am Heart J* 2013;165:964–71.e1.  
54  
55  
56  
57 54 Hajjar LA, Vincent J-L, Galas FRBG, *et al.* Transfusion requirements after cardiac  
58  
59  
60

1  
2  
3 surgery: the TRACS randomized controlled trial. *JAMA* 2010;**304**:1559–67.  
4  
5

6  
7 55 Campbell BCV, Mitchell PJ, Kleinig TJ, *et al.* Endovascular Therapy for Ischemic Stroke  
8 with Perfusion-Imaging Selection. *N Engl J Med* 2015;:150211090353006.  
9  
10

11  
12 56 Goyal M, Demchuk AM, Menon BK, *et al.* Randomized Assessment of Rapid  
13 Endovascular Treatment of Ischemic Stroke. *N Engl J Med* 2015;:150211090353006.  
14  
15

16  
17 57 Butcher KS, Jeerakathil T, Hill M, *et al.* The Intracerebral Hemorrhage Acutely  
18 Decreasing Arterial Pressure Trial. *Stroke* 2013;**44**:620–6.  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29

### 30 **ACKNOWLEDGEMENTS**

31  
32  
33 We would like to thank Dr. Jacques Lacroix from the Canadian Critical Care Trials Group for a  
34 critical review of this manuscript.  
35  
36

37  
38 Dr. Chassé and Lauzier are recipients of a Salary Support Award from the Fonds de Recherche  
39 du Québec - Santé (FRQS). Dr Turgeon is a recipient of a New Investigator Award from the  
40 CIHR.  
41  
42  
43  
44  
45

### 46 **AUTHORS CONTRIBUTIONS**

47  
48  
49 SE, LM, DAF, MC and AFT conceived the project idea. SE, LM, DAF, MC, AFT, LF, DG, AA,  
50 AHK, AT, CL, JS, SM, DD, AB, and GP all contributed substantially to the design of the trial  
51 and drafting of the protocol. SE created the first draft of this submission and all authors have  
52 provided critical review and approve of this final version.  
53  
54  
55  
56  
57  
58  
59  
60

## FUNDING

This work is supported by a Transfusion Science research grant awarded by a Canadian Blood Services and Health Canada in partnership with Canadian Institutes of Health Research (CIHR) Institute of Circulatory and Respiratory Health, competition code 201503OTS.

## 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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

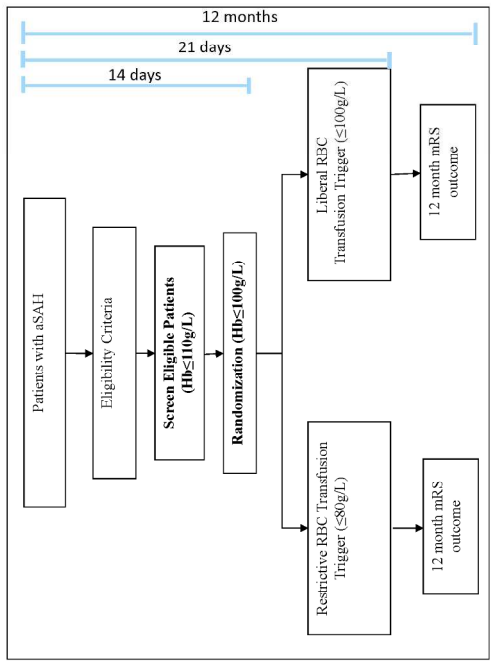


Figure 1: SAHaRA Trial Design  
Figure 1  
215x279mm (300 x 300 DPI)

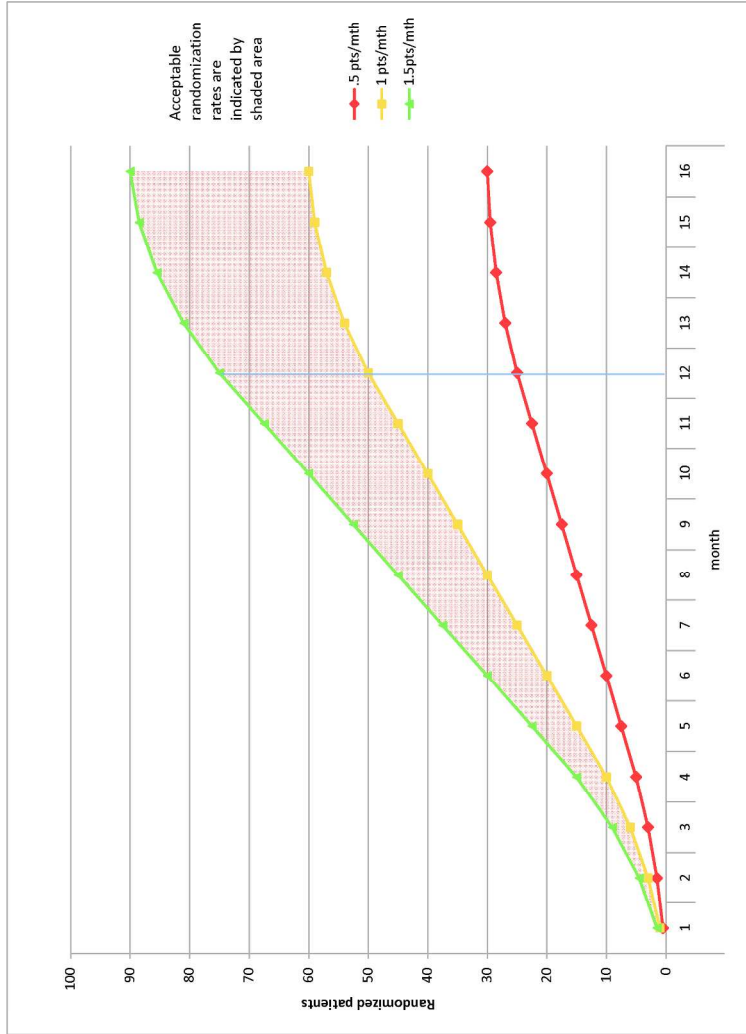


Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation of enrollment

Figure 2  
215x279mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

36/bmjopen-2016-012623 on 7 December 2016. Downloaded from <http://bmjopen.bmj.com/> on April 2, 2024 by guest. Protected by copyright.



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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<u>1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>2</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>2</u>
Protocol version	3	Date and version identifier	<u>          </u>
Funding	4	Sources and types of financial, material, and other support	<u>2, 26</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>1-2</u>
	5b	Name and contact information for the trial sponsor	<u>2</u>
	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	<u>26</u>
	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)	<u>15-16</u>



36/bmjopen-2016-012623 on 7 December 2016. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

**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	<u>5-6, 9-11</u>
	6b	Explanation for choice of comparators	<u>9-11</u>
Objectives	7	Specific objectives or hypotheses	<u>6</u>
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)	<u>6, 8</u>

**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	<u>6</u>
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)	<u>7</u>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>9</u>
	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)	<u>9</u>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>11-13</u>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>14</u>
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	<u>11-14</u>
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)	<u>16-17</u>

36/bmjopen-2016-0-2283 on December 20, 2024 by guest. Protected by copyright. http://bmjopen.bmj.com/ on April 23, 2024

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

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
<b>Methods: Monitoring</b>			
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
<b>Ethics and dissemination</b>			
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)	

36/bmjopen-2016-01-2623 on 7 December 2016. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2022 by guest. Protected by copyright.

1  
2  
3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including  
4 clinical and statistical assumptions supporting any sample size calculations

17

5  
6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size

8, 11

7  
8  
9 **Methods: Assignment of interventions (for controlled trials)**

10 Allocation:

11  
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any  
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
15 or assign interventions

8-9

16  
17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered,  
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

8-9

19  
20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to  
21 interventions

8-9

22 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome  
23 assessors, data analysts), and how

8-9, 13

24  
25 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's  
26 allocated intervention during the trial

N/A

27  
28  
29  
30  
31 **Methods: Data collection, management, and analysis**

32 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related  
33 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
34 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
35 Reference to where data collection forms can be found, if not in the protocol

14, 15, 16

36  
37 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be  
38 collected for participants who discontinue or deviate from intervention protocols

13-14-15

36/bmjopen-2016-02623 on 7 December 2016. Downloaded from http://bmjopen.bmj.com/ on April 29, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>8, 17</u>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>N/A</u>
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	<u>8, 17</u>
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>27-28</u>
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	<u>N/A</u>
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	<u>N/A</u>
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	<u>18, 20</u>
	31b	Authorship eligibility guidelines and any intended use of professional writers	<u>N/A</u>
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>N/A</u>
<b>Appendices</b>			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>N/A</u>
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	<u>N/A</u>

\*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.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-012623.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Jul-2016
Complete List of Authors:	English, Shane; University of Ottawa, Medicine (Critical Care); Ottawa Hospital Research Institute, Clinical Epidemiology Program Fergusson, Dean; Ottawa Hospital Research Institute, Surgery Chassé, Michaël; CHU de Québec, Anesthesiology and Critical Care Turgeon, Alexis; Centre de Recherche du Centre Hospitalier Affilié Universitaire de Québec (CHA), Axe Traumatologie-urgence-soins intensifs, CHA-Hôpital de l'Enfant-Jésus, Université Laval, Anesthesia and Critical Care Medicine; CHU de Québec - Université Laval Research Center, Population Health and Optimal Health Practices Unit (Trauma - Emergency - Critical Care Medicine), Université Laval, Québec City, Québec, Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine Lauzier, Francois Griesdale, Donald; University of British Columbia Algird, Almunder; Hamilton Health Sciences, Neurosurgery Kramer, Andreas H.; Univ Calgary Tinmouth, Alan; Ottawa Hospital Research Institute, Clinical Epidemiology Lum, Cheemun; The Ottawa Hospital, Radiology Sinclair, John; The Ottawa Hospital, Neurosurgery Marshall, Shawn; The Ottawa Hospital, Rehabilitation and Physiatry Dowlatshahi, Dariush; The Ottawa Hospital, Neurology Boutin, A; Université Laval Pagliarello, Giuseppe; The Ottawa Hospital, Surgery McIntyre, Loralyn; Ottawa Hospital Research Institute, Clinical Epidemiology
<b>Primary Subject Heading</b>:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Intensive care
Keywords:	Anaemia < HAEMATOLOGY, Blood bank & transfusion medicine < HAEMATOLOGY, Stroke < NEUROLOGY, NEUROSURGERY, Clinical trials < THERAPEUTICS

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2016-012623 on 7 December 2016. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11 **Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome**  
12 **(SAHaRA): A Pilot Randomized Controlled Trial Protocol**  
13  
14  
15  
16  
17  
18  
19

20 Shane W English<sup>1,2</sup>, D Fergusson<sup>2</sup>, M Chassé<sup>3,4</sup>, AF Turgeon<sup>3,4</sup>, F Lauzier<sup>3,4</sup>, D Griesdale<sup>5</sup>, A  
21 Algird<sup>6</sup>, A Kramer<sup>7,8</sup>, A Tinmouth<sup>2</sup>, C Lum<sup>2</sup>, J Sinclair<sup>2</sup>, S Marshall<sup>2</sup>, D Dowlatshahi<sup>1,2</sup>, A  
22 Boutin<sup>4</sup>, G Pagliarello<sup>2</sup>, and L McIntyre<sup>1,2</sup>, on behalf of the Canadian Critical Care Trials Group.  
23  
24  
25  
26  
27  
28  
29  
30  
31

32 **Affiliation:**

33  
34 <sup>1</sup>Department of Medicine, University of Ottawa, Ottawa Canada

35  
36 <sup>2</sup>Clinical Epidemiology Program (Centre for Transfusion Research), Ottawa Hospital Research  
37 Institute, Ottawa Canada  
38

39  
40 <sup>3</sup>Department of Anesthesiology & Critical Care, Division of Critical Care Medicine, Université  
41 Laval, Québec City, Canada  
42  
43

44  
45 <sup>4</sup>CHU de Québec - Université Laval Research Center, Population Health and Optimal Health  
46 Practices Unit (Trauma - Emergency - Critical Care Medicine), Québec City, Canada  
47  
48

49  
50 <sup>5</sup>Department of Anesthesiology, Pharmacology and Therapeutics, University of British  
51 Columbia, Vancouver, Canada  
52  
53

54  
55 <sup>6</sup>Department of Surgery (Neurosurgery), McMaster University, Hamilton, Canada  
56  
57  
58  
59  
60



<sup>7</sup>Department of Critical Care, University of Calgary, Calgary, Canada

<sup>8</sup>Department of Clinical Neurosciences and the Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

### Correspondence:

Shane English

Department of Medicine (Critical Care), The Ottawa Hospital

Civic Campus Room F202

1053 Carling Avenue

Ottawa ON K1Y 4E9

Canada

613-737-8899 ext. 72818

senglish@ohri.ca

### Funding:

The SAHaRA Pilot Trial is funded by a Transfusion Science research grant awarded by a Canadian Blood Services and Health Canada in partnership with Canadian Institutes of Health Research (CIHR) Institute of Circulatory and Respiratory Health.

**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 ( $Hb \leq 100g/L$ ), comparing a liberal transfusion strategy ( $Hb \leq 100g/L$ ) to a restrictive strategy ( $Hb \leq 80g/L$ ) 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 ( $Hb \leq 110g/L$ ). **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  $\leq 100g/L$ . **Intervention:** Patients will be randomly assigned to either a liberal (threshold:  $Hb \leq 100g/L$ ) or a restrictive transfusion strategy (threshold:  $Hb \leq 80g/L$ ). **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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2016-012623 on 7 December 2016. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

## 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

1  
2  
3 to substantiate these recommendations. Current stated and observed practice from surveys[23]  
4  
5 and our own observational work suggest a more restrictive approach to transfusion (lower  
6  
7 hemoglobin); similar to other critical care patients. However, unlike other critically ill patients,  
8  
9 brain injury and the sequelae that follow (e.g.: vasospasm and delayed cerebral ischemia) may  
10  
11 make these patients more susceptible to the decreased oxygen delivery associated with a lower  
12  
13 transfusion threshold. Considering this obvious paradox and confliction, there is pressing need to  
14  
15 generate high-quality evidence to guide clinical RBC transfusion practices in aSAH. The clinical  
16  
17 impact of varied transfusion thresholds in aSAH has never been studied in a large and rigorous  
18  
19 randomized trial. In collaboration with the Canadian Critical Care Trials Group ([www.ccctg.ca](http://www.ccctg.ca)),  
20  
21 we aim to conduct such an RCT comparing two RBC transfusion strategies in adult patients with  
22  
23 aSAH powered for clinically relevant outcomes. To inform and justify our large trial, we are  
24  
25 conducting a pilot RCT to assess feasibility and strengthen the design of the large-scale trial.  
26  
27  
28  
29  
30  
31  
32  
33

## 34 **METHODS AND ANALYSIS**

### 36 **Study Design**

37  
38 The Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome: A  
39  
40 Pilot Randomized Controlled Trial (SAHaRA Pilot Trial) is a Canadian multicenter (5) open-  
41  
42 label randomized controlled pilot trial in patients with an acute aSAH. To reduce bias from the  
43  
44 open-label design, outcome assessors will be blinded to the treatment assignments.  
45  
46  
47

### 48 **Patient Population**

49  
50 To facilitate randomization into the pilot trial, a subset of patients most likely to meet  
51  
52 randomization criteria will be identified (Screen Eligible Patients). To be screened eligible for  
53  
54 enrolment, patients must meet all inclusion criteria and no exclusion criteria.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Inclusion Criteria:

1. Age  $\geq 18$  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  $\leq 110$ g/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  $\leq 100$  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

1  
2  
3 web interface. Upon meeting the randomization criteria, patients will be randomized in a 1:1  
4  
5 manner to either liberal (intervention) or restrictive (control) RBC transfusion strategy groups. A  
6  
7 schedule of the random treatment allocations, stratified by center will be prepared by an  
8  
9 independent biostatistician at the Coordinating Center. All investigative team members will  
10  
11 remain blinded to the allocation schedules.  
12  
13

### 14 15 **Intervention**

16  
17 Patients fulfilling the eligibility criteria will be randomized to either a liberal or restrictive RBC  
18  
19 transfusion strategy.  
20  
21

#### 22 *Intervention Group: Liberal RBC Transfusion Strategy:*

23  
24 In this intervention group, an RBC transfusion will be triggered by a hemoglobin level of  
25  
26  $\leq 100\text{g/L}$  over the first 21 days in hospital following aSAH.  
27  
28

#### 29 *Control Group: Restrictive RBC Transfusion Strategy*

30  
31 For patients randomized to this group, an RBC transfusion is permitted once a hemoglobin level  
32  
33 of  $\leq 80\text{g/L}$  is observed over the first 21 days in hospital following aSAH. RBC transfusion will  
34  
35 not be mandatory under this threshold, “usual care” rather will prevail, and the decision to and  
36  
37 timing of transfusion will be left to the discretion of the treating team.  
38  
39

#### 40 *Both Groups*

41  
42 All RBC transfusions will be a single unit unless the patient has an active blood loss associated  
43  
44 with hemodynamic instability. In stable non-bleeding patients, a second unit of RBCs should  
45  
46 only be given if a measured post-transfusion hemoglobin level remains below the patient’s  
47  
48 assigned threshold.  
49  
50

#### 51 *Justification of the two triggers*

52  
53 Intervention: Liberal RBC Transfusion Trigger (100g/L): Supported by:  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38
- 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]

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

- 40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 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]

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 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

1  
2  
3 administered; or 2) a repeat hemoglobin is obtained above the allocated threshold within 24  
4  
5 hours of the original measure.  
6

7  
8 Transfusion threshold **non-adherence** will be considered to have occurred with any of the  
9  
10 following: 1) an RBC transfusion occurs before a transfusion threshold is crossed; or 2) in the  
11  
12 liberal arm, a transfusion is not given following a threshold crossing. Transfusion threshold non-  
13  
14 adherence will be considered a *deviation* if: 1) the early transfusion occurs within 5 g/L above  
15  
16 the allocated threshold (eg:  $\leq 105$  g/L for the liberal arm or  $\leq 85$  g/L for the restrictive arm) or, 2)  
17  
18 in the liberal arm, an RBC transfusion does not occur for a hemoglobin measure up to 5 g/L  
19  
20 below the threshold (ie: a transfusion does not occur for a Hb of 95-100 g/L). All other threshold  
21  
22 event non-adherences that are greater or less than 5 g/L for the liberal threshold and greater than  
23  
24 5 g/L below the restrictive threshold will be considered a protocol violation. Transfusion outside  
25  
26 of hemoglobin thresholds for symptomatic anemia or in the event of an active blood loss  
27  
28 associated with hemodynamic instability, as defined by the treating team, will be recorded, but  
29  
30 not considered a protocol violation. Details on non-adherence (date and hemoglobin level prior  
31  
32 to transfusion) and reasons for non-adherence (e.g. physician preference, patient instability,  
33  
34 active bleeding, safety concern) will be recorded.  
35  
36

37  
38  
39 b) *RBC transfusion protocol adherence*: The SAHaRA investigators recognize the importance of  
40  
41 minimizing exposure time below the allocated transfusion threshold and thus every effort shall  
42  
43 be put forth to administer the transfusion expeditiously. For the pilot we endeavor not to exceed  
44  
45 6 hours from transfusion threshold event to transfusion initiation, in keeping with  
46  
47 revascularization time performance measures in stroke literature.[32,33] Median time (and  
48  
49 interquartile range) to RBC transfusion will be described. Transfusion protocol adherence will be  
50  
51 defined as the proportion of RBC transfusions that are initiated within 6 hours. Non-adherence  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 will be considered to have occurred if there is a delay of more than six hours between transfusion  
4 threshold event and transfusion initiation. Transfusions occurring between 6 and 24 hours will be  
5 considered a protocol deviation and greater than 24 hours from the threshold event will be  
6 considered a violation.  
7  
8  
9  
10  
11

12 c) *Clinical outcome ascertainment* will include ability to capture vital status at discharge,  
13 modified Rankin Scale (mRS) score at 6 and 12 months and the Functional Independence  
14 Measure (FIM) and the EuroQOL Quality of Life Scale (EQ5D) at 12 months. The mRS, FIM  
15 and EQ5D will be completed by assessors blinded to participant treatment allocation. Each of  
16 the outcome assessment measures have been selected because they examine different aspects of  
17 the 3 primary levels of body function and stroke rehabilitation (impairment, activity and  
18 participation)[34] and are specifically validated and recommended outcome measures in stroke  
19 research.[35] The mRS is used as the outcome measure over mortality as it includes a spectrum  
20 allowing consideration of severe disability and mortality together as both are highly clinically  
21 significant. Neurologic outcome as assessed by mRS is a common outcome in the aneurysmal  
22 SAH literature[9,18,36–39] and is readily interpretable in this community. It takes <15 minutes  
23 to administer, and can be completed using a structured interview[40–42] or as a telephone  
24 interview.[43] The FIM is a validated[44,45] tool consisting of 18 items that assesses 13  
25 different motor and 5 cognitive tasks previously tested in stroke populations including  
26 aSAH,[44,46] and has an established minimal clinical important difference (MCID) in this  
27 population.[47] It has demonstrated excellent consistency in inter-rater reliability and internal  
28 consistency specifically in neurologic disorder populations. It is easy to administer and is  
29 validated for use by telephone and via proxy respondents.[34] The EQ5D is a short and simple 2-  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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)

<b>Factor</b>	<b>Variable to capture</b>
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  $\geq 3$ , clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of  $\geq 2$  points for  $\geq 2$  hours or new focal neurological deficit)

**B: Co-Interventions**

	<u>Co-Intervention</u>	<u>Variable to capture</u>	<u>Operationalization</u>
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 <sup>31</sup>	-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  $\geq 3$ , clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of  $\geq 2$  points for  $\geq 2$  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**

<b>Assessment:</b>	<b>Baseline:</b>	<b>Prospective – Daily</b>	<b>Hospital Discharge</b>	<b>6 months</b>	<b>12 months</b>
<b>Eligibility Criteria</b>	X				
<b>Recruitment</b>	X				
<b>Informed Consent</b>	X				
<b>Randomization</b>	X				
<b>Baseline Demographics</b>	X				
<b>Medical History</b>	X				
<b>Physical Exam including BP, O<sub>2</sub> sat, GCS</b>	X	X	X		
<b>Baseline labs</b>	X				
<b>aSAH clinical grade</b>	X				
<b>Neuro imaging (U/S, CT, MRI, Angio...)</b>	X				
<b>Vasospasm monitoring (CTA, U/S, angio...) and management</b>	X	X	X		
<b>Laboratory results</b>		X	X		
<b>Transfusion Requirements</b>		X	X		
<b>Co-intervention Log</b>		X	X		
<b>Adherence to treatment</b>		X	X		
<b>AE Review</b>		X	X		
<b>Neurologic outcome (mRS)</b>			X	X	X

<b>Functional Independence Measure (FIM)</b>					X
<b>EuroQOL Quality of Life Scale (EQ5D)</b>					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  $\leq 110$ g/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



1  
2  
3 demonstration of a protocol adherence rate of 90% with a 95% confidence interval of 82.4% to  
4  
5 97.6%.  
6  
7

## 8 **Analytical Plan**

9  
10 **a) Descriptive Analyses:** Baseline characteristics and management data will be presented with  
11 means (continuous measures) or proportions (categorical or ordinal data) with 95%  
12 confidence intervals.  
13  
14

15  
16  
17 **b) Primary Outcome:** Using descriptive statistics, the median randomization rate  
18 (patients/month) overall and per center over the study duration will be calculated and reported  
19 with interquartile range. Only actual months where each center is actively recruiting patients  
20 will be considered in the analysis (i.e.: staggered start up across centers). Figure 2  
21 demonstrates the effect of different randomization rates on study duration and hence  
22 feasibility. A rate of <1 patients/month per center will prompt a site review of the screening  
23 log to examine reasons for missed eligible patients and to discuss how to increase recruitment  
24 rate. Achieving our internal pilot primary objective of a randomization rate of 1.5 patients per  
25 month per center will allow us to complete the large trial in 3.5 years with 10 recruiting  
26 centers.  
27  
28

29  
30  
31 **c) Secondary Outcomes:** Secondary feasibility outcomes will be reported using descriptive  
32 statistics. Protocol adherence will be reported as a proportion as described above. Overall  
33 protocol adherence as well as adherence in the 2 individual study arms will be reported. Given  
34 the internal pilot design, with the plan to include these data in the large trial if no substantial  
35 changes to the protocol are made after the pilot trial, clinical outcomes will be described in  
36 aggregate using descriptive statistics.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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

1  
2  
3 clinically relevant outcomes.[52] Our multi-center design is essential to demonstrate feasibility  
4 of enrollment and randomization into the study and across centers. A 12-month enrollment  
5 period will enable us to determine the feasibility of recruitment at individual centers. Only an  
6 open label design is feasible in a RBC transfusion strategy trial given the inability to blind  
7 bedside clinicians to hemoglobin levels in the safe management of these patients. Similar open  
8 label trial designs have been successfully completed in RBC transfusion trials involving other  
9 patient populations.[22,53–55] Further, prospective randomized open-label blinded end-point  
10 (PROBE) designs have been used in multiple successful, practice-changing stroke trials.[56–58]  
11 To minimize potential bias imposed from open label treatments, our clinical outcome measures  
12 will be completed by a blinded assessor who has not been involved in patient management and is  
13 unaware of treatment assignment. We will demonstrate the feasibility of collecting the proposed  
14 clinical outcomes of the large RCT (neurologic functional outcome using mRS at 6 months and 1  
15 year, as well as the FIM and EQ5D at 1 year) by observing the same follow-up schedule.  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35

36 The results of the SAHaRA internal pilot trial will directly inform the conduct of and guide the  
37 successful completion of the larger RCT. The SAHaRA trial will clarify the role of treating  
38 anemia with RBC transfusion in this unique and vulnerable patient population, and whether that  
39 impacts on functional outcome and mortality. We hypothesize an improvement in outcome with  
40 the treatment of anemia which, if substantiated, would dramatically change the management of  
41 these patients by intensivists, neurologists and neurosurgeons world-wide. A null result would  
42 provide the necessary evidence to the bedside clinician that a restrictive transfusion approach is  
43 safe and prevent the unnecessary risk imposed by blood product transfusion that regularly  
44 occurs.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

- 1 Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. *Neurology* 1998;**50**:1413–8.
- 2 Reed SD, Blough DK, Meyer K, *et al.* Inpatient costs, length of stay, and mortality for cerebrovascular events in community hospitals. *Neurology* 2001;**57**:305–14.
- 3 Nieuwkamp DJ, Setz LE, Algra A, *et al.* Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol* 2009;**8**:635–42.
- 4 Le Roux PD. Anemia and transfusion after subarachnoid hemorrhage. *Neurocrit Care* 2011;**15**:342–53.
- 5 Springer M V, Schmidt JM, Wartenberg KE, *et al.* Predictors of global cognitive impairment 1 year after subarachnoid hemorrhage. *Neurosurgery* 2009;**65**:1043–50; discussion 1050–1.
- 6 Sampson TR, Dhar R, Diringer MN. Factors associated with the development of anemia after subarachnoid hemorrhage. *Neurocrit Care* 2010;**12**:4–9.
- 7 Naidech AM, Drescher J, Ault ML, *et al.* Higher hemoglobin is associated with less cerebral infarction, poor outcome, and death after subarachnoid hemorrhage. *Neurosurgery* 2006;**59**:775–9.
- 8 Wartenberg KE, Mayer SA. Medical complications after subarachnoid hemorrhage: new

- 1  
2  
3 strategies for prevention and management. *Curr Opin Crit Care* 2006;**12**:78–84.  
4  
5  
6  
7 9 Naidech AM, Jovanovic B, Wartenberg KE, *et al.* Higher hemoglobin is associated with  
8 improved outcome after subarachnoid hemorrhage. *Crit Care Med* 2007;**35**:2383–9.  
9  
10  
11 10 Kramer AH, Gurka MJ, Nathan B, *et al.* Complications associated with anemia and blood  
12 transfusion in patients with aneurysmal subarachnoid hemorrhage. *Crit Care Med*  
13 2008;**36**:2070–5.  
14  
15  
16  
17 11 Kramer AH, Zygun DA. Anemia and red blood cell transfusion in neurocritical care. *Crit*  
18 *Care* 2009;**13**:R89.  
19  
20  
21  
22  
23  
24  
25  
26 12 Amin M, Fergusson D, Wilson K, *et al.* The societal unit cost of allogenic red blood cells  
27 and red blood cell transfusion in Canada. *Transfusion* 2004;**44**:1479–86.  
28  
29  
30  
31  
32 13 Smith MJ, Le Roux PD, Elliott JP, *et al.* Blood transfusion and increased risk for  
33 vasospasm and poor outcome after subarachnoid hemorrhage. *J Neurosurg* 2004;**101**:1–7.  
34  
35  
36  
37 14 Broessner G, Lackner P, Hoefler C, *et al.* Influence of red blood cell transfusion on  
38 mortality and long-term functional outcome in 292 patients with spontaneous  
39 subarachnoid hemorrhage. *Crit Care Med* 2009;**37**:1886–92.  
40  
41  
42  
43  
44  
45 15 Levine J, Kofke A, Cen L, *et al.* Red blood cell transfusion is associated with infection  
46 and extracerebral complications after subarachnoid hemorrhage. *Neurosurgery*  
47 2010;**66**:312–8; discussion 318.  
48  
49  
50  
51  
52  
53 16 C. Taylor, K. Gough, J. Gross MS. Transfusion threshold for acute aneurysmal  
54 subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 2012;**24**:254–5.  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 17 E. Mauricio, M. Robinson, J. Dajac, O. Gajic EF. Anemia, transfusion thresholds and  
5  
6 incidence of vasospasm and infarction among patients with aneurysmal subarachnoid  
7  
8 hemorrhage. *Crit Care Med* 2010;**38**:A86.  
9  
10  
11 18 Naidech AM, Shaibani A, Garg RK, *et al.* Prospective, randomized trial of higher goal  
12  
13 hemoglobin after subarachnoid hemorrhage. *Neurocrit Care* 2010;**13**:313–20.  
14  
15  
16 19 Connolly ES, Rabinstein AA, Carhuapoma JR, *et al.* Guidelines for the management of  
17  
18 aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the  
19  
20 American Heart Association/American Stroke Association. *Stroke* 2012;**43**:1711–37.  
21  
22  
23 20 Diringner MN, Bleck TP, Claude Hemphill J, *et al.* Critical care management of patients  
24  
25 following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical  
26  
27 Care Society’s Multidisciplinary Consensus Conference. *Neurocrit Care* 2011;**15**:211–40.  
28  
29  
30 21 Lacroix J, Hébert PC, Hutchison JS, *et al.* Transfusion strategies for patients in pediatric  
31  
32 intensive care units. *N Engl J Med* 2007;**356**:1609–19.  
33  
34  
35 22 Hébert PC, Wells G, Blajchman MA, *et al.* A multicenter, randomized, controlled clinical  
36  
37 trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care  
38  
39 Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;**340**:409–17.  
40  
41  
42 23 Kramer AH, Diringner MN, Suarez JI, *et al.* Red blood cell transfusion in patients with  
43  
44 subarachnoid hemorrhage: a multidisciplinary North American survey. *Crit Care*  
45  
46 2011;**15**:R30.  
47  
48  
49 24 Kramer AH, Zygun D a, Bleck TP, *et al.* Relationship between hemoglobin concentrations  
50  
51 and outcomes across subgroups of patients with aneurysmal subarachnoid hemorrhage.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- Neurocrit Care* 2009;**10**:157–65.
- 25 English SW, Chasse M, Turgeon A, *et al.* Aneurysmal subarachnoid hemorrhage and anemia: a canadian multi-centre retrospective cohort study. *Crit Care* 2016;**20**:P337.
- 26 Dhar R, Scalfani MT, Zazulia AR, *et al.* Comparison of induced hypertension, fluid bolus, and blood transfusion to augment cerebral oxygen delivery after subarachnoid hemorrhage. *J Neurosurg* 2012;**116**:648–56.
- 27 Smith MJ, Stiefel MF, Magge S, *et al.* Packed red blood cell transfusion increases local cerebral oxygenation. *Crit Care Med* 2005;**33**:1104–8.
- 28 Kurtz P, Helbok R, Claassen J, *et al.* Effect of packed red blood cell transfusion on cerebral oxygenation and metabolism after subarachnoid hemorrhage. *Crit Care* 2010;**14**:P341.
- 29 Dhar R, Zazulia AR, Videen TO, *et al.* Red blood cell transfusion increases cerebral oxygen delivery in anemic patients with subarachnoid hemorrhage. *Stroke* (00392499) 2009;**40**:3039–44.
- 30 Kurtz P, Schmidt JM, Claassen J, *et al.* Anemia is associated with metabolic distress and brain tissue hypoxia after subarachnoid hemorrhage. *Neurocrit Care* 2010;**13**:10–6.
- 31 English SW, Chasse M, Turgeon A, *et al.* Red blood cell transfusion in aneurysmal subarachnoid hemorrhage – the Sahara cohort study. *Crit Care* 2016;**20**:P336.
- 32 Jauch EC, Saver JL, Adams HP, *et al.* Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;**44**:870–947.

- 1  
2  
3  
4 33 Lindsay M, Gubitz G, Bayley M, *et al.* Canadian Best Practice Recommendations for  
5 Stroke Care (Update 2010). Ottawa ON Canada: 2010.  
6  
7  
8  
9 34 Salter K, Campbell N, Richardson M, *et al.* Outcome Measures in Stroke Rehabilitation.  
10 In: *Evidence Based Research in Stroke Rehabilitation*. 2013. 1–144.  
11  
12  
13  
14 35 Sullivan JE, Crouner BE, Kluding PM, *et al.* Outcome measures for individuals with  
15 stroke: process and recommendations from the American Physical Therapy Association  
16 neurology section task force. *Phys Ther* 2013;**93**:1383–96.  
17  
18  
19  
20  
21  
22 36 Hop JW, Rinkel GJ, Algra A, *et al.* Case-fatality rates and functional outcome after  
23 subarachnoid hemorrhage: a systematic review. *Stroke* 1997;**28**:660–4.  
24  
25  
26  
27  
28 37 Nieuwkamp DJ, De Gans K, Rinkel GJ, *et al.* Treatment and outcome of severe  
29 intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a  
30 systematic review of the literature. *J Neurol* 2000;**247**:117–21.  
31  
32  
33  
34  
35  
36 38 Kirkpatrick PJ, Turner CL, Smith C, *et al.* Simvastatin in aneurysmal subarachnoid  
37 haemorrhage (STASH): a multicentre randomised phase 3 trial. *Lancet Neurol*  
38 2014;**13**:666–75.  
39  
40  
41  
42  
43  
44 39 Dorhout Mees SM, Algra A, Vandertop WP, *et al.* Magnesium for aneurysmal  
45 subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet*  
46 2012;**380**:44–9.  
47  
48  
49  
50  
51  
52 40 Banks JL, Marotta C a. Outcomes validity and reliability of the modified Rankin scale:  
53 implications for stroke clinical trials: a literature review and synthesis. *Stroke*  
54 2007;**38**:1091–6.  
55  
56  
57  
58  
59  
60



- 1  
2  
3 41 Wilson JTL, Hareendran A, Hendry A, *et al.* Reliability of the modified Rankin Scale  
4 across multiple raters: benefits of a structured interview. *Stroke* 2005;**36**:777–81.  
5  
6  
7  
8  
9 42 Wilson JTL. Improving the Assessment of Outcomes in Stroke: Use of a Structured  
10 Interview to Assign Grades on the Modified Rankin Scale. *Stroke* 2002;**33**:2243–6.  
11  
12  
13  
14 43 Savio K, Luca G, Pietra D, *et al.* Reliability of the modified Rankin Scale applied by  
15 telephone. *Neurol Int* 2013;**5**:6–7.  
16  
17  
18  
19  
20 44 O’Dell MW, Watanabe TK, De Roos ST, *et al.* Functional outcome after inpatient  
21 rehabilitation in persons with subarachnoid hemorrhage. *Arch Phys Med Rehabil*  
22 2002;**83**:678–82.  
23  
24  
25  
26  
27  
28 45 Linacre JM, Heinemann AW, Wright BD, *et al.* The structure and stability of the  
29 Functional Independence Measure. *Arch Phys Med Rehabil* 1994;**75**:127–32.  
30  
31  
32  
33 46 Dromerick AW, Edwards DF, Diringner MN. Sensitivity to changes in disability after  
34 stroke: a comparison of four scales useful in clinical trials. *J Rehabil Res Dev*;**40**:1–8.  
35  
36  
37  
38  
39 47 Beninato M, Gill-Body KM, Salles S, *et al.* Determination of the minimal clinically  
40 important difference in the FIM instrument in patients with stroke. *Arch Phys Med*  
41 *Rehabil* 2006;**87**:32–9.  
42  
43  
44  
45  
46  
47 48 Wartenberg KE, Schmidt JM, Claassen J, *et al.* Impact of medical complications on  
48 outcome after subarachnoid hemorrhage. *Crit Care Med* 2006;**34**:617–23; quiz 624.  
49  
50  
51  
52  
53 49 Rodriguez DR, Matamoros CS, Fernandez LC, *et al.* Factors associated with poor  
54 outcome for aneurysmal subarachnoid hemorrhage in a series of 334 patients. *Neurologia*  
55 2015;Epub:1–7.  
56  
57  
58  
59  
60

- 1  
2  
3  
4 50 Molyneux AJ, Kerr RSC, Yu L, *et al.* International subarachnoid aneurysm trial (ISAT) of  
5 neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured  
6 intracranial aneurysms: a randomised comparison of effects on survival, dependency,  
7 seizures, rebleeding, subgroups, and . *Lancet* 2005;**366**:809–17.  
8  
9  
10  
11  
12  
13  
14 51 Geocadin RG, Bleck TP, Koroshetz WJ, *et al.* Research priorities in neurocritical care.  
15 *Neurocrit Care* 2012;**16**:35–41.  
16  
17  
18  
19 52 Thabane L, Ma J, Chu R, *et al.* A tutorial on pilot studies : the what , why and how. *BMC*  
20 *Med Res Methodol* 2010;**10**:1–10.  
21  
22  
23  
24  
25 53 Carson JL, Terrin ML, Noveck H, *et al.* Liberal or restrictive transfusion in high-risk  
26 patients after hip surgery. *N Engl J Med* 2011;**365**:2453–62.  
27  
28  
29  
30 54 Carson JL, Brooks MM, Abbott JD, *et al.* Liberal versus restrictive transfusion thresholds  
31 for patients with symptomatic coronary artery disease. *Am Heart J* 2013;**165**:964–71.e1.  
32  
33  
34  
35  
36 55 Hajjar LA, Vincent J-L, Galas FRBG, *et al.* Transfusion requirements after cardiac  
37 surgery: the TRACS randomized controlled trial. *JAMA* 2010;**304**:1559–67.  
38  
39  
40  
41 56 Campbell BCV, Mitchell PJ, Kleinig TJ, *et al.* Endovascular Therapy for Ischemic Stroke  
42 with Perfusion-Imaging Selection. *N Engl J Med* 2015;**372**:1009-1018.  
43  
44  
45  
46  
47 57 Goyal M, Demchuk AM, Menon BK, *et al.* Randomized Assessment of Rapid  
48 Endovascular Treatment of Ischemic Stroke. *N Engl J Med* 2015;**372**:1019-1030.  
49  
50  
51  
52  
53 58 Butcher KS, Jeerakathil T, Hill M, *et al.* The Intracerebral Hemorrhage Acutely  
54 Decreasing Arterial Pressure Trial. *Stroke* 2013;**44**:620–6.  
55  
56  
57  
58  
59  
60

## ACKNOWLEDGEMENTS

We would like to thank Dr. Jacques Lacroix from the Canadian Critical Care Trials Group for a critical review of this manuscript.

Dr. Chassé and Lauzier are recipients of a Salary Support Award from the Fonds de Recherche du Québec - Santé (FRQS). Dr Turgeon is a recipient of a New Investigator Award from the CIHR.

## 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.

## FUNDING

This work is supported by a Transfusion Science research grant awarded by a Canadian Blood Services and Health Canada in partnership with Canadian Institutes of Health Research (CIHR) Institute of Circulatory and Respiratory Health, competition code 201503OTS.

## 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

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

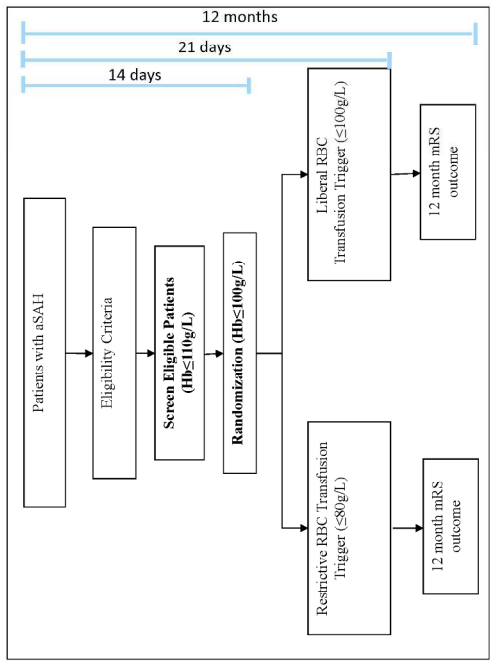


Figure 1: SAHaRA Trial Design  
Figure 1  
215x279mm (300 x 300 DPI)

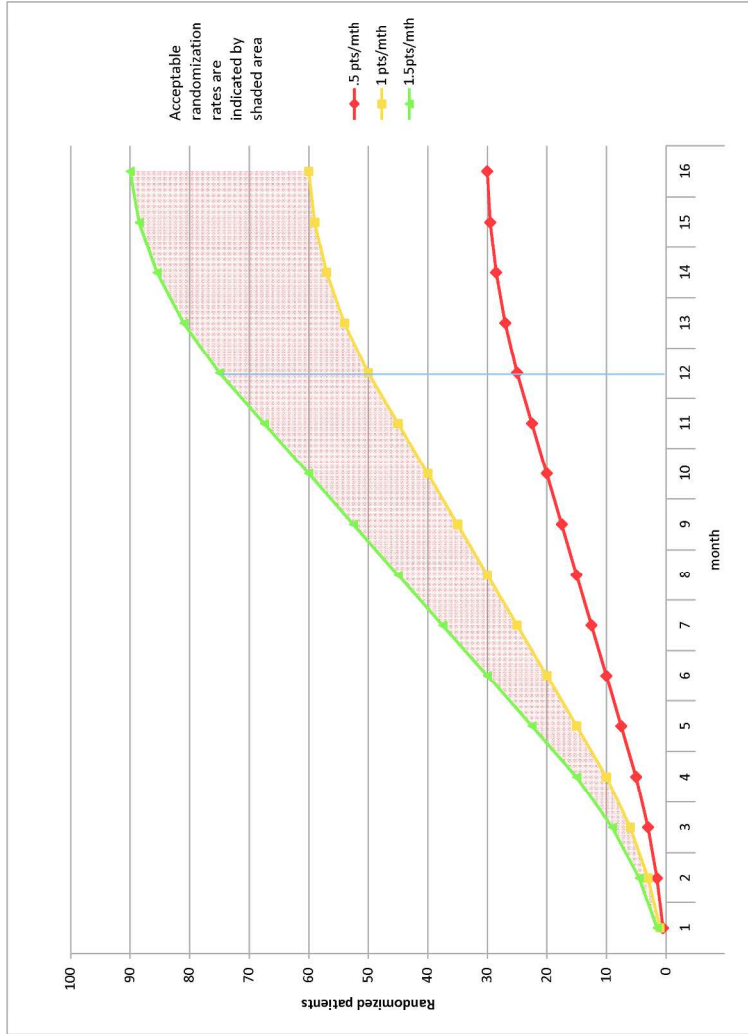


Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation of enrollment

Figure 2  
215x279mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

36/bmjopen-2016-012623 on 7 December 2016. Downloaded from http://bmjopen.bmj.com/ on April 2, 2024 by guest. Protected by copyright.



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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<u>1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>2</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>2</u>
Protocol version	3	Date and version identifier	<u>          </u>
Funding	4	Sources and types of financial, material, and other support	<u>2, 26</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>1-2</u>
	5b	Name and contact information for the trial sponsor	<u>2</u>
	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	<u>26</u>
	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)	<u>15-16</u>

36/bmjopen-2016-012623 on 7 December 2016. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

**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	<u>5-6, 9-11</u>
	6b	Explanation for choice of comparators	<u>9-11</u>
Objectives	7	Specific objectives or hypotheses	<u>6</u>
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)	<u>6, 8</u>

**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	<u>6</u>
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)	<u>7</u>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>9</u>
	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)	<u>9</u>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>11-13</u>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>14</u>
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	<u>11-14</u>
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)	<u>16-17</u>



36/bmjopen-2016-0-2283 on December 20, 2024 by guest. Protected by copyright. http://bmjopen.bmj.com/ on April 23, 2024

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

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
<b>Methods: Monitoring</b>			
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
<b>Ethics and dissemination</b>			
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)	

1  
2  
3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including  
4 clinical and statistical assumptions supporting any sample size calculations

17

5  
6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size

8, 11

7  
8  
9 **Methods: Assignment of interventions (for controlled trials)**

10 Allocation:

11  
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any  
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
15 or assign interventions

8-9

16  
17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered,  
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

8-9

19  
20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to  
21 interventions

8-9

22  
23 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome  
24 assessors, data analysts), and how

8-9, 13

25  
26 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's  
27 allocated intervention during the trial

N/A

28  
29  
30  
31 **Methods: Data collection, management, and analysis**

32  
33 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related  
34 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
36 Reference to where data collection forms can be found, if not in the protocol

14, 15, 16

37  
38 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be  
39 collected for participants who discontinue or deviate from intervention protocols

13-14-15

36/bmjopen-2016-01-2623 on 7 December 2016. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2022 by guest. Protected by copyright.

36/bmjopen-2016-02623 on 7 December 2016. Downloaded from http://bmjopen.bmj.com/ on April 29, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>8, 17</u>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>N/A</u>
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	<u>8, 17</u>
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>27-28</u>
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	<u>N/A</u>
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	<u>N/A</u>
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	<u>18, 20</u>
	31b	Authorship eligibility guidelines and any intended use of professional writers	<u>N/A</u>
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>N/A</u>
<b>Appendices</b>			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>N/A</u>
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	<u>N/A</u>

\*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.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-012623.R2
Article Type:	Protocol
Date Submitted by the Author:	04-Oct-2016
Complete List of Authors:	English, Shane; University of Ottawa, Medicine (Critical Care); Ottawa Hospital Research Institute, Clinical Epidemiology Program Fergusson, Dean; Ottawa Hospital Research Institute, Surgery Chassé, Michaël; CHU de Québec, Anesthesiology and Critical Care Turgeon, Alexis; Centre de Recherche du Centre Hospitalier Affilié Universitaire de Québec (CHA), Axe Traumatologie-urgence-soins intensifs, CHA-Hôpital de l'Enfant-Jésus, Université Laval, Anesthesia and Critical Care Medicine; CHU de Québec - Université Laval Research Center, Population Health and Optimal Health Practices Unit (Trauma - Emergency - Critical Care Medicine), Université Laval, Québec City, Québec, Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine Lauzier, Francois Griesdale, Donald; University of British Columbia Algird, Almunder; Hamilton Health Sciences, Neurosurgery Kramer, Andreas H.; Univ Calgary Tinmouth, Alan; Ottawa Hospital Research Institute, Clinical Epidemiology Lum, Cheemun; The Ottawa Hospital, Radiology Sinclair, John; The Ottawa Hospital, Neurosurgery Marshall, Shawn; The Ottawa Hospital, Rehabilitation and Physiatry Dowlatshahi, Dariush; The Ottawa Hospital, Neurology Boutin, A; Université Laval Pagliarello, Giuseppe; The Ottawa Hospital, Surgery McIntyre, Loralyn; Ottawa Hospital Research Institute, Clinical Epidemiology
<b>Primary Subject Heading</b>:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Intensive care
Keywords:	Anaemia < HAEMATOLOGY, Blood bank & transfusion medicine < HAEMATOLOGY, Stroke < NEUROLOGY, NEUROSURGERY, Clinical trials < THERAPEUTICS

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2016-012623 on 7 December 2016. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3 1  
4  
5 2  
6  
7  
8 3  
9  
10 4 **Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome**  
11 **(SAHaRA): A Pilot Randomized Controlled Trial Protocol**  
12  
13 5  
14  
15 6  
16  
17 7  
18

19  
20 8 Shane W English<sup>1,2</sup>, D Fergusson<sup>2</sup>, M Chassé<sup>3,4</sup>, AF Turgeon<sup>5,6</sup>, F Lauzier<sup>5,6,7</sup>, D Griesdale<sup>8</sup>, A  
21  
22 9 Algird<sup>9</sup>, A Kramer<sup>10,11</sup>, A Tinmouth<sup>2,12</sup>, C Lum<sup>2</sup>, J Sinclair<sup>2</sup>, S Marshall<sup>2</sup>, D Dowlathshahi<sup>2,12</sup>, A  
23  
24 10 Boutin<sup>6</sup>, G Pagliarello<sup>2</sup>, and LA McIntyre<sup>1,2</sup>, on behalf of the Canadian Critical Care Trials  
25  
26  
27 11 Group.  
28  
29 12  
30  
31 13  
32  
33

34 14 **Affiliation:**

35  
36 15 <sup>1</sup>Department of Medicine (Critical Care), University of Ottawa, Ottawa Canada

37  
38 16 <sup>2</sup>Clinical Epidemiology Program (Centre for Transfusion Research), Ottawa Hospital Research  
39  
40  
41 17 Institute, Ottawa Canada

42  
43 18 <sup>3</sup>Centre Hospitalier Universitaire de Montréal Research Center, Evaluation, Care Systems and  
44  
45  
46 19 Services Theme, Montréal, Canada

47  
48 20 <sup>4</sup>Department of Medicine (Critical Care), Centre Hospitalier Universitaire de Montréal,  
49  
50 21 Montréal, Canada

51  
52 22 <sup>5</sup>Department of Anesthesiology & Critical Care, Division of Critical Care Medicine, Université  
53  
54  
55 23 Laval, Québec City, Canada  
56  
57  
58  
59  
60

- 1  
2  
3 24 <sup>6</sup>CHU de Québec - Université Laval Research Center, Population Health and Optimal Health  
4  
5  
6 25 Practices Unit (Trauma - Emergency - Critical Care Medicine), Québec City, Canada  
7  
8 26 <sup>7</sup>Department of Medicine, Université Laval, Québec City, Canada  
9  
10 27 <sup>8</sup>Department of Anesthesiology, Pharmacology and Therapeutics, University of British  
11  
12 28 Columbia, Vancouver, Canada  
13  
14 29 <sup>9</sup>Department of Surgery (Neurosurgery), McMaster University, Hamilton, Canada  
15  
16  
17 30 <sup>10</sup>Department of Critical Care, University of Calgary, Calgary, Canada  
18  
19  
20 31 <sup>11</sup>Department of Clinical Neurosciences and the Hotchkiss Brain Institute, University of Calgary,  
21  
22 32 Calgary, Canada  
23  
24 33 <sup>12</sup>Department of Medicine, University of Ottawa, Ottawa Canada  
25  
26  
27 34

28  
29 **Correspondence:**  
30

31 36 Shane English

32 37 Department of Medicine (Critical Care), The Ottawa Hospital

33 38 Civic Campus Room F202

34 39 1053 Carling Avenue

35 40 Ottawa ON K1Y 4E9

36 41 Canada

37 42 613-737-8899 ext. 72818

38 43 senglish@ohri.ca  
39  
40  
41  
42  
43  
44  
45

46  
47  
48  
49  
50  
51  
52  
53 **Funding:**  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 46 The SAHaRA Pilot Trial is funded by a Transfusion Science research grant awarded by  
4  
5  
6 47 Canadian Blood Services and Health Canada in partnership with the Canadian Institutes of  
7  
8 48 Health Research (CIHR) Institute of Circulatory and Respiratory Health.  
9

10  
11 49

12  
13 50 **Trial Registry No.:** NCT 02483351 (clinicaltrials.gov registered June 25, 2015)  
14

15 51 **Key Words:** aneurysm, erythrocyte, subarachnoid hemorrhage, red blood cell transfusion,  
16  
17 52 randomized controlled trial  
18

19  
20 53 **Word count** – Article: 3982 Abstract: 295  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 54 ABSTRACT

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

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

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

1  
2  
3 77 RCT comparing 2 RBC transfusion strategies examining the effect of a liberal strategy on 12-  
4  
5 78 month outcome following aSAH. (Trial Registry No.: NCT 02483351)  
6  
7  
8 79  
9

10  
11 80 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
12

- 13 81 • Rigorous trial methodology to evaluate the feasibility of conducting a larger trial to  
14 82 establish optimal red blood cell transfusion thresholds in patients with aneurysmal  
15 83 subarachnoid hemorrhage  
16  
17 84 • The multi-center pragmatic design strengthens future results and generalizability  
18 85 • To minimize any potential bias from the necessary open-label design, collection of co-  
19 86 interventions and blinded outcome-assessment are being undertaken  
20  
21 87 • The pilot trial was not designed to test clinically relevant outcomes  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 88 INTRODUCTION

89 Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating illness caused by the  
90 spontaneous rupture of a weakened and enlarged artery in the brain. It affects a young population  
91 and is a significant cause of premature death and loss of potential life years, at a similar  
92 magnitude of ischemic stroke.[1] It is a common neurologic reason for intensive care unit (ICU)  
93 admission[2] and is associated with a mortality rate of about 35% in North America (range 20-  
94 70%).[3] Less than one third afflicted make a full recovery[4] and 20% of survivors experience  
95 significant morbidity[5] having an impact on daily living.

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

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

1  
2  
3 111 to substantiate these recommendations. Current stated and observed practice from surveys[23]  
4  
5 112 and our own observational work suggest a more restrictive approach to transfusion (lower  
6  
7  
8 113 hemoglobin); similar to other critical care patients. However, unlike other critically ill patients,  
9  
10 114 brain injury and the sequelae that follow (e.g.: vasospasm and delayed cerebral ischemia) may  
11  
12 115 make these patients more susceptible to the decreased oxygen delivery associated with a lower  
13  
14 116 transfusion threshold. Considering this obvious paradox and confliction, there is pressing need to  
15  
16 117 generate high-quality evidence to guide clinical RBC transfusion practices in aSAH. The clinical  
17  
18 118 impact of varied transfusion thresholds in aSAH has never been studied in a large and rigorous  
19  
20 119 randomized trial. In collaboration with the Canadian Critical Care Trials Group ([www.ccctg.ca](http://www.ccctg.ca)),  
21  
22 120 we aim to conduct such an RCT comparing two RBC transfusion strategies in adult patients with  
23  
24 121 aSAH powered for clinically relevant outcomes. To inform and justify our large trial, we are  
25  
26 122 conducting a pilot RCT to assess feasibility and strengthen the design of the large-scale trial.  
27  
28  
29  
30  
31  
32  
33

## 34 124 **METHODS AND ANALYSIS**

### 36 125 **Study Design**

37  
38 126 The Aneurysmal SubArachnoid Hemorrhage - Red Blood Cell Transfusion And Outcome: A  
39 127 Pilot Randomized Controlled Trial (SAHaRA Pilot Trial) is a multicenter open-label randomized  
40  
41 128 controlled pilot trial in patients with an acute aSAH at 5 Canadian academic tertiary care  
42  
43 129 hospitals. To reduce bias from the open-label design, outcome assessors will be blinded to the  
44  
45 130 treatment assignments.  
46  
47  
48  
49

### 51 131 **Objectives**

52  
53 132 Primary Objective: To evaluate the feasibility of reaching an optimal randomization rate of at  
54  
55 133 least 1 patient per month per center over the pilot trial period.  
56  
57  
58  
59  
60

1  
2  
3 134 Secondary Objectives:1) To evaluate the feasibility of obtaining: a) at least 90% adherence to the  
4  
5 135 allocated study transfusion thresholds; b) at least 90% adherence to the study RBC transfusion  
6  
7 136 protocol; and c)  $\geq 95\%$  clinical outcomes measures (modified Rankin Scale [mRS], Functional  
8  
9 137 Independence Measure [FIM] and EuroQOL Quality of Life Scale [EQ5D]) at 6 and 12 months.

### 138 **Patient Population**

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

#### 142 Inclusion Criteria:

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

#### 152 Exclusion Criteria:

- 153 1. Physician and or next of kin decision to withdraw/withhold critical care at time of  
154 enrolment
- 155 2. Active bleeding with hemodynamic instability at time of enrolment
- 156 3. Patients with contraindication or known objection to blood transfusions

1  
2  
3 157 4. SAH due to causes other than saccular aneurysm rupture including mycotic, traumatic  
4  
5 158 and dissecting aneurysms, and aneurysms associated with arteriovenous malformations  
6  
7

8 159 Our exclusion criteria are in place to prevent enrolling patients who: 1) would not benefit from  
9  
10 160 the intervention; 2) object to the intervention; and/or 3) have sustained a bleed due to  
11  
12 161 mechanistically different causes whose pathophysiological properties are not necessarily shared  
13  
14 162 with aSAH.  
15

16 163 Screen eligible patients who experience an incident Hb  $\leq$ 100 g/L within 14 days  
17  
18 164 following aSAH will be randomized.  
19

20  
21  
22 165 **Randomization and Allocation Concealment:**  
23

24 166 Figure 1 provides a schematic description of the trial design. Local research coordinators will  
25  
26 167 screen each patient admitted to either the intensive care unit, intermediate care unit or step-down  
27  
28 168 unit (where applicable) or neurosurgical inpatient unit in the setting of aSAH for up to 14 days  
29  
30 169 after the qualifying bleed. Enrolment and randomization over 14 days is necessary as previous  
31  
32 170 work has demonstrated that the negative effect on outcome was most pronounced in patients with  
33  
34 171 anemia between days 6 and 11.[24] Further, our observational study demonstrated that 95% of  
35  
36 172 incident anemia occurred within the first 14 days, and that 97.4% did so while admitted to a  
37  
38 173 high-acuity unit.[25] The risk of new onset vasospasm, a significant threat to morbidity and  
39  
40 174 mortality in this population is highly unlikely to begin after 14 days but its duration may surpass  
41  
42 175 this period.[19] A Screen Eligible period is essential to focus study resources on the group of  
43  
44 176 patients most likely to be randomized, to capture the first occurrence of anemia (to *minimize* any  
45  
46 177 exposure time below their allocated transfusion threshold) and to optimize the randomization  
47  
48 178 rate. The study team will screen daily hemoglobin values (or more frequent as clinically  
49  
50 179 indicated and/or as deemed by treating team) of Screen Eligible Patients.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 180 Patients meeting eligibility criteria (or their substitute decision maker) will be approached for  
4  
5  
6 181 consent by the site research coordinator in accordance with standard local procedures as  
7  
8 182 approved by each local REB and in accordance with Good Clinical Practice. A mixed consent  
9  
10 183 model (a priori and deferred consent models), pending on local REB approval, will be used. A  
11  
12 184 web-based randomization system maintained at the Coordinating Center will be used to allocate  
13  
14 185 treatment assignments. Under the guidance of the site principal investigator or research  
15  
16 186 coordinator, the participant's eligibility criteria will again be confirmed with a checklist using a  
17  
18 187 web interface. Upon meeting the randomization criteria, patients will be randomized in a 1:1  
19  
20 188 manner to either liberal (intervention) or restrictive (control) RBC transfusion strategy groups. A  
21  
22 189 schedule of the random treatment allocations, stratified by center will be prepared by an  
23  
24 190 independent biostatistician at the Coordinating Center. All investigative team members will  
25  
26 191 remain blinded to the allocation schedules.  
27  
28  
29  
30

## 31 192 **Intervention**

32 193 Patients fulfilling the eligibility criteria will be randomized to either a liberal or restrictive RBC  
33  
34 194 transfusion strategy.  
35  
36  
37

### 38 195 *Intervention Group: Liberal RBC Transfusion Strategy:*

39 196 In this intervention group, an RBC transfusion will be triggered by a hemoglobin level of  
40  
41 197  $\leq 100\text{g/L}$  over the first 21 days in hospital following aSAH.  
42  
43  
44

### 45 198 *Control Group: Restrictive RBC Transfusion Strategy*

46 199 For patients randomized to this group, an RBC transfusion is permitted once a hemoglobin level  
47  
48 200 of  $\leq 80\text{g/L}$  is observed over the first 21 days in hospital following aSAH. RBC transfusion will  
49  
50 201 not be mandatory under this threshold, "usual care" rather will prevail, and the decision to and  
51  
52 202 timing of transfusion will be left to the discretion of the treating team.  
53  
54  
55  
56  
57  
58  
59  
60



203 *Both Groups*

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

208 *Justification of the two triggers*

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

- 210 a) Physiologic evidence that RBC transfusion increases oxygen delivery and cerebral  
211 tissue oxygen tension.[26–28]
- 212 b) Amongst SAH patients with hemoglobin <110g/L, compared to induced hypertension  
213 and fluid bolus, RBC transfusion was the only intervention demonstrated to  
214 significantly reduce (47%) the number of cerebral regions with low oxygen delivery  
215 per patient. Amongst those with low global oxygen delivery, RBC transfusion resulted  
216 in a significant larger rise in global oxygen delivery.[26]
- 217 c) A small physiologic study of aSAH patients (N=8) demonstrated stable cerebral blood  
218 flow, an increase in oxygen delivery and a decrease in the oxygen extraction fraction  
219 with an RBC transfusion at a hemoglobin level of <100 g/L.[29]
- 220 d) A hemoglobin level of <100g/L was associated with brain tissue hypoxia and metabolic  
221 distress compared to those with hemoglobin >100g/L.[30]
- 222 e) The maximum threshold hemoglobin to trigger RBC transfusion in the context of a  
223 study amongst the 531 intensivists, neurointensivists and neurosurgeons surveyed was  
224 100g/L. [23]

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

- 1  
2  
3 226 a) In a survey of 531 practicing intensivists, neurointensivists and neurosurgeons in North  
4  
5 227 America the median hemoglobin to trigger a transfusion ranged from 75 to 80g/L  
6  
7  
8 228 depending on SAH grade. [23]  
9  
10 229 b) Amongst practicing intensivists, neurointensivists and neurosurgeons the lowest  
11  
12 230 acceptable threshold hemoglobin to trigger a RBC transfusion was 70g/L in >70% of  
13  
14 231 respondents. [23]  
15  
16 232 c) A Canadian multi-center observational study (N=434) conducted in 4 academic centers in  
17  
18 233 2012 and 2013 completed by the SAHaRA study team demonstrated that the median pre-  
19  
20 234 transfusion hemoglobin was 79g/L (IQR 74-93g/L).[31]  
21  
22 235 A transfusion trigger of 100g/L has previously been shown to be safe in an aSAH  
23  
24 236 population.[18] The allocated transfusion strategy will be applied from the time of randomization  
25  
26 237 to day 21 after the original bleed, death or hospital discharge, whichever comes first. The first 21  
27  
28 238 days following aSAH represents the period of greatest vulnerability to the direct consequences of  
29  
30 239 aSAH, and the sequelae, including vasospasm, that follow.  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 241 **Outcomes**

### 242 *Primary outcome*

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

1  
2  
3 248 outcome is objective, readily measurable, and feasible based on data generated from a cohort  
4  
5 249 study conducted by the authors.  
6  
7

8 250 *Secondary outcomes*

9  
10 251 a) *Transfusion threshold adherence* will be described as the proportion of “per protocol” RBC  
11  
12 252 transfusion *events*. A transfusion threshold event is defined as an occurrence which starts when a  
13  
14 253 hemoglobin value is measured at or below the allocated threshold for the first time since the  
15  
16 254 previous event and ends when one of the following occurs: 1) an RBC transfusion is  
17  
18 255 administered; or 2) a repeat hemoglobin is obtained above the allocated threshold within 24  
19  
20 256 hours of the original measure.  
21  
22  
23

24 257 Transfusion threshold **non-adherence** will be considered to have occurred with any of the  
25  
26 258 following: 1) an RBC transfusion occurs before a transfusion threshold is crossed; or 2) in the  
27  
28 259 liberal arm, a transfusion is not given following a threshold crossing. Transfusion threshold non-  
29  
30 260 adherence will be considered a *deviation* if: 1) the early transfusion occurs within 5 g/L above  
31  
32 261 the allocated threshold (eg:  $\leq 105$  g/L for the liberal arm or  $\leq 85$  g/L for the restrictive arm) or, 2)  
33  
34 262 in the liberal arm, an RBC transfusion does not occur for a hemoglobin measure up to 5 g/L  
35  
36 263 below the threshold (ie: a transfusion does not occur for a Hb of 95-100 g/L). All other threshold  
37  
38 264 event non-adherences that are greater or less than 5 g/L for the liberal threshold and greater than  
39  
40 265 5 g/L below the restrictive threshold will be considered a protocol violation. Transfusion outside  
41  
42 266 of hemoglobin thresholds for symptomatic anemia or in the event of an active blood loss  
43  
44 267 associated with hemodynamic instability, as defined by the treating team, will be recorded, but  
45  
46 268 not considered a protocol violation. Details on non-adherence (date and hemoglobin level prior  
47  
48 269 to transfusion) and reasons for non-adherence (e.g. physician preference, patient instability,  
49  
50 270 active bleeding, safety concern) will be recorded.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 271 b) *RBC transfusion protocol adherence*: The SAHaRA investigators recognize the importance of  
4  
5 272 minimizing exposure time below the allocated transfusion threshold and thus every effort shall  
6  
7  
8 273 be put forth to administer the transfusion expeditiously. For the pilot we endeavor not to exceed  
9  
10 274 6 hours from transfusion threshold event to transfusion initiation, in keeping with  
11  
12 275 revascularization time performance measures in stroke literature.[32,33] Median time (and  
13  
14 276 interquartile range) to RBC transfusion will be described. Transfusion protocol adherence will be  
15  
16 277 defined as the proportion of RBC transfusions that are initiated within 6 hours. Non-adherence  
17  
18 278 will be considered to have occurred if there is a delay of more than six hours between transfusion  
19  
20 279 threshold event and transfusion initiation. Transfusions occurring between 6 and 24 hours will be  
21  
22 280 considered a protocol deviation and greater than 24 hours from the threshold event will be  
23  
24 281 considered a violation.

25  
26  
27  
28  
29 282 c) *Clinical outcome ascertainment* will include ability to capture vital status at discharge,  
30  
31 283 modified Rankin Scale (mRS) score at 6 and 12 months and the Functional Independence  
32  
33 284 Measure (FIM) and the EuroQOL Quality of Life Scale (EQ5D) at 12 months. The mRS, FIM  
34  
35 285 and EQ5D will be completed by assessors blinded to participant treatment allocation. Each of  
36  
37 286 the outcome assessment measures have been selected because they examine different aspects of  
38  
39 287 the 3 primary levels of body function and stroke rehabilitation (impairment, activity and  
40  
41 288 participation)[34] and are specifically validated and recommended outcome measures in stroke  
42  
43 289 research.[35] The mRS is used as the outcome measure over mortality as it includes a spectrum  
44  
45 290 allowing consideration of severe disability and mortality together as both are highly clinically  
46  
47 291 significant. Neurologic outcome as assessed by mRS is a common outcome in the aneurysmal  
48  
49 292 SAH literature[9,18,36–39] and is readily interpretable in this community. It takes <15 minutes  
50  
51 293 to administer, and can be completed using a structured interview[40–42] or as a telephone  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 294 interview.[43] The FIM is a validated[44,45] tool consisting of 18 items that assesses 13  
4  
5 295 different motor and 5 cognitive tasks previously tested in stroke populations including  
6  
7  
8 296 aSAH,[44,46] and has an established minimal clinical important difference (MCID) in this  
9  
10 297 population.[47] It has demonstrated excellent consistency in inter-rater reliability and internal  
11  
12 298 consistency specifically in neurologic disorder populations. It is easy to administer and is  
13  
14 299 validated for use by telephone and via proxy respondents.[34] The EQ5D is a short and simple 2-  
15  
16 300 part questionnaire that may be self-administered, completed by interview or via a proxy  
17  
18 301 respondent, and is used to value and describe health states.[34]

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

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

### 314 **Table 1: Important baseline characteristics and co-interventions to be prospectively** 315 **collected**

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

<b>Factor</b>	<b>Variable to capture</b>
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  $\geq 3$ , clinical vasospasm requires the radiographic diagnosis with clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of  $\geq 2$  points for  $\geq 2$  hours or new focal neurological deficit)

### B: Co-Interventions

	<b>Co-Intervention</b>	<b>Variable to capture</b>	<b>Operationalization</b>
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 <sup>31</sup>	-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),

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

331  
 332 Descriptive metrics will be used to measure feasibility including the primary outcome of  
 333 randomization rate. These data will be gathered prospectively at each study center by a trained  
 334 and qualified study nurse or practitioner using an electronic case report form. The number of  
 335 eligible but not enrolled patients will be tracked, and reasons for non-enrollment will be  
 336 recorded. Protocol adherence will be assessed prospectively by trained study personnel and all  
 337 episodes of non-adherence to protocol will be adjudicated by 3 members of the steering  
 338 committee, blinded to clinical outcome. Protocol adherence will be reported as a ratio of total  
 339 correct transfusion threshold events to a combination of total number of transfusion events  
 340 (needed or not needed per protocol) and total number of missed transfusion non-adherence  
 341 events. Feasibility of outcome assessment will be measured by the ability to obtain the defined  
 342 outcome measures at the pre-specified time periods. The three outcome measurement  
 343 instruments (mRS, FIM and EQ5D) will be implemented by a trained and qualified study  
 344 coordinator blinded to the intervention according the defined schedule (Table 2). Vital status at  
 345 discharge and adverse events will be captured using a case report form prospectively by the site  
 346 investigator or the research coordinator.

347 **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 <sub>2</sub> sat, GCS	X	X	X		

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

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

### 350 **Executive and Steering Committee Roles and Responsibilities**

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

### 361 **Ethics, Confidentiality and Data Monitoring Body**



1  
2  
3 362 The study protocol has been approved by the host center (Ottawa Health Science Network  
4  
5 363 Research Ethics Board (REB) - OHSN-REB 20150433-01H). The **intervention and control** arm  
6  
7  
8 364 of the trial are part of usual care in many centers, and thus the research risk to participants is  
9  
10 365 minimal. Safety considerations are addressed within the protocol, and allow for individualized  
11  
12 366 care where needed. In addition to potentially intervention-related adverse event reporting, pre-  
13  
14 367 defined expected adverse events will be prospectively monitored and include acute respiratory  
15  
16 368 distress syndrome, cardiovascular failure, cardiac ischemia/infarction, venous thromboembolic  
17  
18 369 events, septic shock, hospital acquired infections and transfusion reactions.  
19

20  
21  
22 370 All participant data will be de-identified to ensure confidentiality and through the assignment  
23  
24 371 of an anonymous identifier by the web-based randomization tool and data collection form. All  
25  
26 372 data will be collected and stored in firewall-protected, secure servers at the host center according  
27  
28 373 to institutional and REB policy and in accordance with Good Clinical Practice.  
29

30  
31 374 A three-member independent Data Safety Monitoring Committee (DSMC) has been  
32  
33 375 assembled and will oversee the progression of ascertaining the pilot objectives and all trial safety  
34  
35 376 aspects according to a prescribed schedule, DSMC Charter and GCP reporting.  
36  
37

### 38 377 **Sample Size**

39  
40 378 A sample size of 60 patients will allow us to evaluate enrolment rate averaging 1.5 patients per  
41  
42 379 month per center with 5 centers over a 1-year study period. Based on our cohort study, we expect  
43  
44 380 that 90 eligible patients will need to be screened into the study to achieve a randomized sample  
45  
46 381 of 60 patients (that is more than 2/3 of patients with a hemoglobin of  $\leq 110$ g/L had a nadir of  
47  
48 382 100g/L or less). All 5 proposed pilot trial sites are academic tertiary care centres with  
49  
50 383 approximately 60-120 aSAH admissions per year. Our sample size will also allow the  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 384 demonstration of a protocol adherence rate of 90% with a 95% confidence interval of 82.4% to  
4  
5 385 97.6%.

7  
8 386 **Analytical Plan**

9  
10 387 **a) Descriptive Analyses:** Baseline characteristics and management data will be presented with  
11  
12 388 means (continuous measures) or proportions (categorical or ordinal data) with 95%  
13  
14 389 confidence intervals.

15  
16  
17 390 **b) Primary Outcome:** Using descriptive statistics, the median randomization rate  
18  
19 391 (patients/month) overall and per center over the study duration will be calculated and reported  
20  
21 392 with interquartile range. Only actual months where each center is actively recruiting patients  
22  
23 393 will be considered in the analysis (i.e.: staggered start up across centers). Figure 2  
24  
25 394 demonstrates the effect of different randomization rates on study duration and hence  
26  
27 395 feasibility. A rate of <1 patients/month per center will prompt a site review of the screening  
28  
29 396 log to examine reasons for missed eligible patients and to discuss how to increase recruitment  
30  
31 397 rate. Achieving our internal pilot primary objective of a randomization rate of 1.5 patients per  
32  
33 398 month per center will allow us to complete the large trial in 3.5 years with 10 recruiting  
34  
35 399 centers.

36  
37  
38  
39  
40 400 **c) Secondary Outcomes:** Secondary feasibility outcomes will be reported using descriptive  
41  
42 401 statistics. Protocol adherence will be reported as a proportion as described above. Overall  
43  
44 402 protocol adherence as well as adherence in the 2 individual study arms will be reported. Given  
45  
46 403 the internal pilot design, with the plan to include these data in the large trial if no substantial  
47  
48 404 changes to the protocol are made after the pilot trial, clinical outcomes will be described in  
49  
50 405 aggregate using descriptive statistics.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 406 **Study Timeline**

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

## 412 **Dissemination**

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

## 418 **DISCUSSION**

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

1  
2  
3 430 editorials and practice guidelines.[15,19,20,51] The uncritical use of variable thresholds does not  
4  
5  
6 431 advance patient outcome or physician practice.  
7

8 432

9  
10 433 Accomplishing the feasibility objectives of this pilot trial will ensure the successful completion

11  
12 434 of the future large trial. A pilot trial powered to feasibility outcomes is the essential initial step in

13  
14 435 the preparation for and eventual successful completion of the more costly larger trial, powered to

15  
16  
17 436 clinically relevant outcomes.[52] Our multi-center design is essential to demonstrate feasibility

18  
19  
20 437 of enrollment and randomization into the study and across centers. A 12-month enrollment

21  
22 438 period will enable us to determine the feasibility of recruitment at individual centers. Only an

23  
24 439 open label design is feasible in a RBC transfusion strategy trial given the inability to blind

25  
26 440 bedside clinicians to hemoglobin levels in the safe management of these patients. Similar open

27  
28  
29 441 label trial designs have been successfully completed in RBC transfusion trials involving other

30  
31  
32 442 patient populations.[22,53–55] Further, prospective randomized open-label blinded end-point

33  
34 443 (PROBE) designs have been used in multiple successful, practice-changing stroke trials.[56–58]

35  
36 444 To minimize potential bias imposed from open label treatments, our clinical outcome measures

37  
38 445 will be completed by a blinded assessor who has not been involved in patient management and is

39  
40 446 unaware of treatment assignment. We will demonstrate the feasibility of collecting the proposed

41  
42 447 clinical outcomes of the large RCT (neurologic functional outcome using mRS at 6 months and 1

43  
44 448 year, as well as the FIM and EQ5D at 1 year) by observing the same follow-up schedule.  
45

46  
47 449

48  
49  
50 450 The results of the SAHaRA internal pilot trial will directly inform the conduct of and guide the

51  
52 451 successful completion of the larger RCT. The SAHaRA trial will clarify the role of treating

53  
54 452 anemia with RBC transfusion in this unique and vulnerable patient population, and whether that  
55

56  
57  
58  
59  
60

1  
2  
3 453 impacts on functional outcome and mortality. We hypothesize an improvement in outcome with  
4  
5 454 the treatment of anemia which, if substantiated, would dramatically change the management of  
6  
7  
8 455 these patients by intensivists, neurologists and neurosurgeons world-wide. A null result would  
9  
10 456 provide the necessary evidence to the bedside clinician that a restrictive transfusion approach is  
11  
12  
13 457 safe and prevent the unnecessary risk imposed by blood product transfusion that regularly  
14  
15 458 occurs.  
16  
17  
18 459

## 20 460 REFERENCES

- 21  
22  
23  
24 461 1 Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from  
25  
26 462 subarachnoid hemorrhage. *Neurology* 1998;**50**:1413–8.
- 27  
28  
29 463 2 Reed SD, Blough DK, Meyer K, *et al.* Inpatient costs, length of stay, and mortality for  
30  
31 464 cerebrovascular events in community hospitals. *Neurology* 2001;**57**:305–14.
- 32  
33  
34  
35 465 3 Nieuwkamp DJ, Setz LE, Algra A, *et al.* Changes in case fatality of aneurysmal  
36  
37 466 subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis.  
38  
39 467 *Lancet Neurol* 2009;**8**:635–42.
- 40  
41  
42  
43 468 4 Le Roux PD. Anemia and transfusion after subarachnoid hemorrhage. *Neurocrit Care*  
44  
45 469 2011;**15**:342–53.
- 46  
47  
48  
49 470 5 Springer M V, Schmidt JM, Wartenberg KE, *et al.* Predictors of global cognitive  
50  
51 471 impairment 1 year after subarachnoid hemorrhage. *Neurosurgery* 2009;**65**:1043–50;  
52  
53 472 discussion 1050–1.
- 54  
55  
56  
57 473 6 Sampson TR, Dhar R, Diringer MN. Factors associated with the development of anemia  
58  
59  
60

- 1  
2  
3 474 after subarachnoid hemorrhage. *Neurocrit Care* 2010;**12**:4–9.  
4  
5  
6  
7 475 7 Naidech AM, Drescher J, Ault ML, *et al.* Higher hemoglobin is associated with less  
8  
9 476 cerebral infarction, poor outcome, and death after subarachnoid hemorrhage.  
10  
11 477 *Neurosurgery* 2006;**59**:775–9.  
12  
13  
14 478 8 Wartenberg KE, Mayer SA. Medical complications after subarachnoid hemorrhage: new  
15  
16 479 strategies for prevention and management. *Curr Opin Crit Care* 2006;**12**:78–84.  
17  
18  
19  
20 480 9 Naidech AM, Jovanovic B, Wartenberg KE, *et al.* Higher hemoglobin is associated with  
21  
22 481 improved outcome after subarachnoid hemorrhage. *Crit Care Med* 2007;**35**:2383–9.  
23  
24  
25  
26 482 10 Kramer AH, Gurka MJ, Nathan B, *et al.* Complications associated with anemia and blood  
27  
28 483 transfusion in patients with aneurysmal subarachnoid hemorrhage. *Crit Care Med*  
29  
30 484 2008;**36**:2070–5.  
31  
32  
33  
34 485 11 Kramer AH, Zygun DA. Anemia and red blood cell transfusion in neurocritical care. *Crit*  
35  
36 486 *Care* 2009;**13**:R89.  
37  
38  
39 487 12 Amin M, Fergusson D, Wilson K, *et al.* The societal unit cost of allogenic red blood cells  
40  
41 488 and red blood cell transfusion in Canada. *Transfusion* 2004;**44**:1479–86.  
42  
43  
44  
45 489 13 Smith MJ, Le Roux PD, Elliott JP, *et al.* Blood transfusion and increased risk for  
46  
47 490 vasospasm and poor outcome after subarachnoid hemorrhage. *J Neurosurg* 2004;**101**:1–7.  
48  
49  
50  
51 491 14 Broessner G, Lackner P, Hoefler C, *et al.* Influence of red blood cell transfusion on  
52  
53 492 mortality and long-term functional outcome in 292 patients with spontaneous  
54  
55 493 subarachnoid hemorrhage. *Crit Care Med* 2009;**37**:1886–92.  
56  
57  
58  
59  
60

- 1  
2  
3 494 15 Levine J, Kofke A, Cen L, *et al.* Red blood cell transfusion is associated with infection  
4  
5 and extracerebral complications after subarachnoid hemorrhage. *Neurosurgery*  
6 495  
7 2010;**66**:312–8; discussion 318.  
8 496  
9  
10  
11 497 16 C. Taylor, K. Gough, J. Gross MS. Transfusion threshold for acute aneurysmal  
12  
13 subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 2012;**24**:254–5.  
14 498  
15  
16  
17 499 17 E. Mauricio, M. Robinson, J. Dajac, O. Gajic EF. Anemia, transfusion thresholds and  
18  
19 incidence of vasospasm and infarction among patients with aneurysmal subarachnoid  
20 500  
21 hemorrhage. *Crit Care Med* 2010;**38**:A86.  
22 501  
23  
24  
25 502 18 Naidech AM, Shaibani A, Garg RK, *et al.* Prospective, randomized trial of higher goal  
26  
27 hemoglobin after subarachnoid hemorrhage. *Neurocrit Care* 2010;**13**:313–20.  
28 503  
29  
30  
31 504 19 Connolly ES, Rabinstein AA, Carhuapoma JR, *et al.* Guidelines for the management of  
32  
33 aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the  
34 505  
35 American Heart Association/American Stroke Association. *Stroke* 2012;**43**:1711–37.  
36 506  
37  
38  
39 507 20 Diringer MN, Bleck TP, Claude Hemphill J, *et al.* Critical care management of patients  
40  
41 following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical  
42 508  
43 Care Society’s Multidisciplinary Consensus Conference. *Neurocrit Care* 2011;**15**:211–40.  
44 509  
45  
46  
47 510 21 Lacroix J, Hébert PC, Hutchison JS, *et al.* Transfusion strategies for patients in pediatric  
48  
49 intensive care units. *N Engl J Med* 2007;**356**:1609–19.  
50 511  
51  
52  
53 512 22 Hébert PC, Wells G, Blajchman MA, *et al.* A multicenter, randomized, controlled clinical  
54  
55 trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care  
56 513  
57 Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;**340**:409–17.  
58 514  
59  
60

- 1  
2  
3 515 23 Kramer AH, Diringner MN, Suarez JI, *et al.* Red blood cell transfusion in patients with  
4  
5  
6 516 subarachnoid hemorrhage: a multidisciplinary North American survey. *Crit Care*  
7  
8 517 2011;**15**:R30.  
9  
10  
11 518 24 Kramer AH, Zygun D a, Bleck TP, *et al.* Relationship between hemoglobin concentrations  
12  
13 519 and outcomes across subgroups of patients with aneurysmal subarachnoid hemorrhage.  
14  
15 520 *Neurocrit Care* 2009;**10**:157–65.  
16  
17  
18  
19 521 25 English SW, Chasse M, Turgeon A, *et al.* Aneurysmal subarachnoid hemorrhage and  
20  
21 522 anemia: a canadian multi-centre retrospective cohort study. *Crit Care* 2016;**20**:P337.  
22  
23  
24 523 26 Dhar R, Scalfani MT, Zazulia AR, *et al.* Comparison of induced hypertension, fluid bolus,  
25  
26 524 and blood transfusion to augment cerebral oxygen delivery after subarachnoid  
27  
28 525 hemorrhage. *J Neurosurg* 2012;**116**:648–56.  
29  
30  
31  
32 526 27 Smith MJ, Stiefel MF, Magge S, *et al.* Packed red blood cell transfusion increases local  
33  
34 527 cerebral oxygenation. *Crit Care Med* 2005;**33**:1104–8.  
35  
36  
37  
38 528 28 Kurtz P, Helbok R, Claassen J, *et al.* Effect of packed red blood cell transfusion on  
39  
40 529 cerebral oxygenation and metabolism after subarachnoid hemorrhage. *Crit Care*  
41  
42 530 2010;**14**:P341.  
43  
44  
45  
46 531 29 Dhar R, Zazulia AR, Videen TO, *et al.* Red blood cell transfusion increases cerebral  
47  
48 532 oxygen delivery in anemic patients with subarachnoid hemorrhage. *Stroke* (00392499)  
49  
50 533 2009;**40**:3039–44.  
51  
52  
53  
54 534 30 Kurtz P, Schmidt JM, Claassen J, *et al.* Anemia is associated with metabolic distress and  
55  
56 535 brain tissue hypoxia after subarachnoid hemorrhage. *Neurocrit Care* 2010;**13**:10–6.  
57  
58  
59  
60



- 1  
2  
3 536 31 English SW, Chasse M, Turgeon A, *et al.* Red blood cell transfusion in aneurysmal  
4  
5  
6 537 subarachnoid hemorrhage – the Sahara cohort study. *Crit Care* 2016;**20**:P336.  
7  
8  
9 538 32 Jauch EC, Saver JL, Adams HP, *et al.* Guidelines for the early management of patients  
10  
11 539 with acute ischemic stroke: a guideline for healthcare professionals from the American  
12  
13 540 Heart Association/American Stroke Association. *Stroke* 2013;**44**:870–947.  
14  
15  
16  
17 541 33 Lindsay M, Gubitz G, Bayley M, *et al.* Canadian Best Practice Recommendations for  
18  
19 542 Stroke Care (Update 2010). Ottawa ON Canada: 2010.  
20  
21  
22 543 34 Salter K, Campbell N, Richardson M, *et al.* Outcome Measures in Stroke Rehabilitation.  
23  
24 544 In: *Evidence Based Research in Stroke Rehabilitation*. 2013. 1–144.  
25  
26  
27  
28 545 35 Sullivan JE, Crowner BE, Kluding PM, *et al.* Outcome measures for individuals with  
29  
30 546 stroke: process and recommendations from the American Physical Therapy Association  
31  
32 547 neurology section task force. *Phys Ther* 2013;**93**:1383–96.  
33  
34  
35  
36 548 36 Hop JW, Rinkel GJ, Algra A, *et al.* Case-fatality rates and functional outcome after  
37  
38 549 subarachnoid hemorrhage: a systematic review. *Stroke* 1997;**28**:660–4.  
39  
40  
41 550 37 Nieuwkamp DJ, De Gans K, Rinkel GJ, *et al.* Treatment and outcome of severe  
42  
43 551 intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a  
44  
45 552 systematic review of the literature. *J Neurol* 2000;**247**:117–21.  
46  
47  
48  
49 553 38 Kirkpatrick PJ, Turner CL, Smith C, *et al.* Simvastatin in aneurysmal subarachnoid  
50  
51 554 haemorrhage (STASH): a multicentre randomised phase 3 trial. *Lancet Neurol*  
52  
53 555 2014;**13**:666–75.  
54  
55  
56  
57 556 39 Dorhout Mees SM, Algra A, Vandertop WP, *et al.* Magnesium for aneurysmal  
58  
59  
60

- 1  
2  
3 557 subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. *Lancet*  
4  
5  
6 558 2012;**380**:44–9.  
7  
8  
9 559 40 Banks JL, Marotta C a. Outcomes validity and reliability of the modified Rankin scale:  
10  
11 560 implications for stroke clinical trials: a literature review and synthesis. *Stroke*  
12  
13 561 2007;**38**:1091–6.  
14  
15  
16  
17 562 41 Wilson JTL, Hareendran A, Hendry A, *et al*. Reliability of the modified Rankin Scale  
18  
19 563 across multiple raters: benefits of a structured interview. *Stroke* 2005;**36**:777–81.  
20  
21  
22  
23 564 42 Wilson JTL. Improving the Assessment of Outcomes in Stroke: Use of a Structured  
24  
25 565 Interview to Assign Grades on the Modified Rankin Scale. *Stroke* 2002;**33**:2243–6.  
26  
27  
28 566 43 Savio K, Luca G, Pietra D, *et al*. Reliability of the modified Rankin Scale applied by  
29  
30 567 telephone. *Neurol Int* 2013;**5**:6–7.  
31  
32  
33  
34 568 44 O’Dell MW, Watanabe TK, De Roos ST, *et al*. Functional outcome after inpatient  
35  
36 569 rehabilitation in persons with subarachnoid hemorrhage. *Arch Phys Med Rehabil*  
37  
38 570 2002;**83**:678–82.  
39  
40  
41  
42 571 45 Linacre JM, Heinemann AW, Wright BD, *et al*. The structure and stability of the  
43  
44 572 Functional Independence Measure. *Arch Phys Med Rehabil* 1994;**75**:127–32.  
45  
46  
47 573 46 Dromerick AW, Edwards DF, Diringner MN. Sensitivity to changes in disability after  
48  
49 574 stroke: a comparison of four scales useful in clinical trials. *J Rehabil Res Dev*;**40**:1–8.  
50  
51  
52  
53 575 47 Beninato M, Gill-Body KM, Salles S, *et al*. Determination of the minimal clinically  
54  
55 576 important difference in the FIM instrument in patients with stroke. *Arch Phys Med*  
56  
57 577 *Rehabil* 2006;**87**:32–9.  
58  
59  
60

- 1  
2  
3 578 48 Wartenberg KE, Schmidt JM, Claassen J, *et al.* Impact of medical complications on  
4  
5  
6 579 outcome after subarachnoid hemorrhage. *Crit Care Med* 2006;**34**:617–23; quiz 624.  
7  
8  
9 580 49 Rodriguez DR, Matamoros CS, Fernandez LC, *et al.* Factors associated with poor  
10  
11 581 outcome for aneurysmal subarachnoid hemorrhage in a series of 334 patients. *Neurologia*  
12  
13 582 2015;Epub:1–7.  
14  
15  
16  
17 583 50 Molyneux AJ, Kerr RSC, Yu L, *et al.* International subarachnoid aneurysm trial (ISAT) of  
18  
19 584 neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured  
20  
21 585 intracranial aneurysms: a randomised comparison of effects on survival, dependency,  
22  
23 586 seizures, rebleeding, subgroups, and . *Lancet* 2005;**366**:809–17.  
24  
25  
26  
27 587 51 Geocadin RG, Bleck TP, Koroshetz WJ, *et al.* Research priorities in neurocritical care.  
28  
29 588 *Neurocrit Care* 2012;**16**:35–41.  
30  
31  
32  
33 589 52 Thabane L, Ma J, Chu R, *et al.* A tutorial on pilot studies : the what , why and how. *BMC*  
34  
35 590 *Med Res Methodol* 2010;**10**:1–10.  
36  
37  
38 591 53 Carson JL, Terrin ML, Noveck H, *et al.* Liberal or restrictive transfusion in high-risk  
39  
40 592 patients after hip surgery. *N Engl J Med* 2011;**365**:2453–62.  
41  
42  
43  
44 593 54 Carson JL, Brooks MM, Abbott JD, *et al.* Liberal versus restrictive transfusion thresholds  
45  
46 594 for patients with symptomatic coronary artery disease. *Am Heart J* 2013;**165**:964–71.e1.  
47  
48  
49 595 55 Hajjar LA, Vincent J-L, Galas FRBG, *et al.* Transfusion requirements after cardiac  
50  
51 596 surgery: the TRACS randomized controlled trial. *JAMA* 2010;**304**:1559–67.  
52  
53  
54  
55 597 56 Campbell BCV, Mitchell PJ, Kleinig TJ, *et al.* Endovascular Therapy for Ischemic Stroke  
56  
57 598 with Perfusion-Imaging Selection. *N Engl J Med* 2015;**372**:1009-1018.  
58  
59  
60

1  
2  
3 599 57 Goyal M, Demchuk AM, Menon BK, *et al.* Randomized Assessment of Rapid  
4  
5 600 Endovascular Treatment of Ischemic Stroke. *N Engl J Med* 2015;**372**:1019-1030.  
6  
7

8  
9 601 58 Butcher KS, Jeerakathil T, Hill M, *et al.* The Intracerebral Hemorrhage Acutely  
10  
11 602 Decreasing Arterial Pressure Trial. *Stroke* 2013;**44**:620–6.  
12  
13

14 603

15 604

## 20 605 **ACKNOWLEDGEMENTS**

21  
22  
23  
24 606 We would like to thank Dr. Jacques Lacroix from the Canadian Critical Care Trials Group for a  
25  
26 607 critical review of this manuscript. We also wish to acknowledge the administrative support Ms.  
27  
28 608 Marnie Gordon and Mr. Irwin Schweitzer.  
29  
30

31  
32 609 Dr. Chassé and Lauzier are recipients of a Salary Support Award from the Fonds de Recherche  
33  
34 610 du Québec - Santé (FRQS). Dr Turgeon is a recipient of a New Investigator Award from the  
35  
36 611 CIHR.  
37  
38

## 39 612 **AUTHORS CONTRIBUTIONS**

40  
41  
42  
43 613 SE, LM, DAF, MC and AFT conceived the project idea. SE, LM, DAF, MC, AFT, LF, DG, AA,  
44  
45 614 AHK, AT, CL, JS, SM, DD, AB, and GP all contributed substantially to the design of the trial  
46  
47 615 and drafting of the protocol. SE created the first draft of this submission and all authors have  
48  
49 616 provided critical review and approve of this final version.  
50  
51

## 52 617 **FUNDING**

1  
2  
3 618 This work is supported by a Transfusion Science research grant awarded by a Canadian Blood  
4  
5 619 Services and Health Canada in partnership with Canadian Institutes of Health Research (CIHR)  
6  
7  
8 620 Institute of Circulatory and Respiratory Health, competition code 201503OTS.  
9  
10

11 621 **COMPETING INTERESTS**  
12

13  
14 622 None.  
15  
16

17  
18 623 **FIGURE LEGEND**  
19

20  
21 624 Figure 1: SAHaRA Trial Design  
22

23 625 Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation  
24  
25 626 of enrollment  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

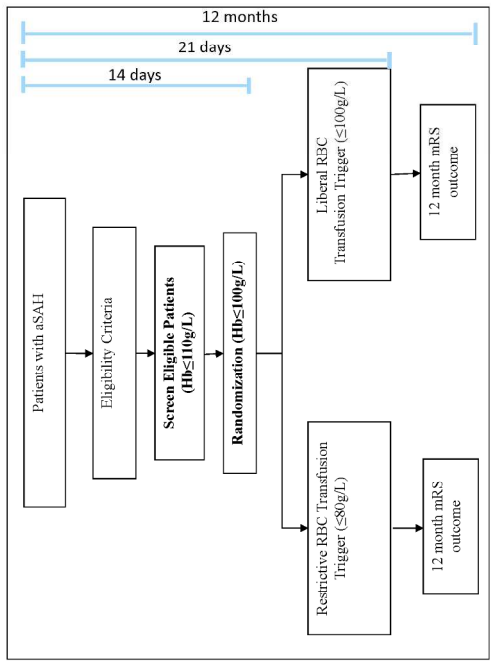


Figure 1: SAHaRA Trial Design  
Figure 1  
215x279mm (300 x 300 DPI)

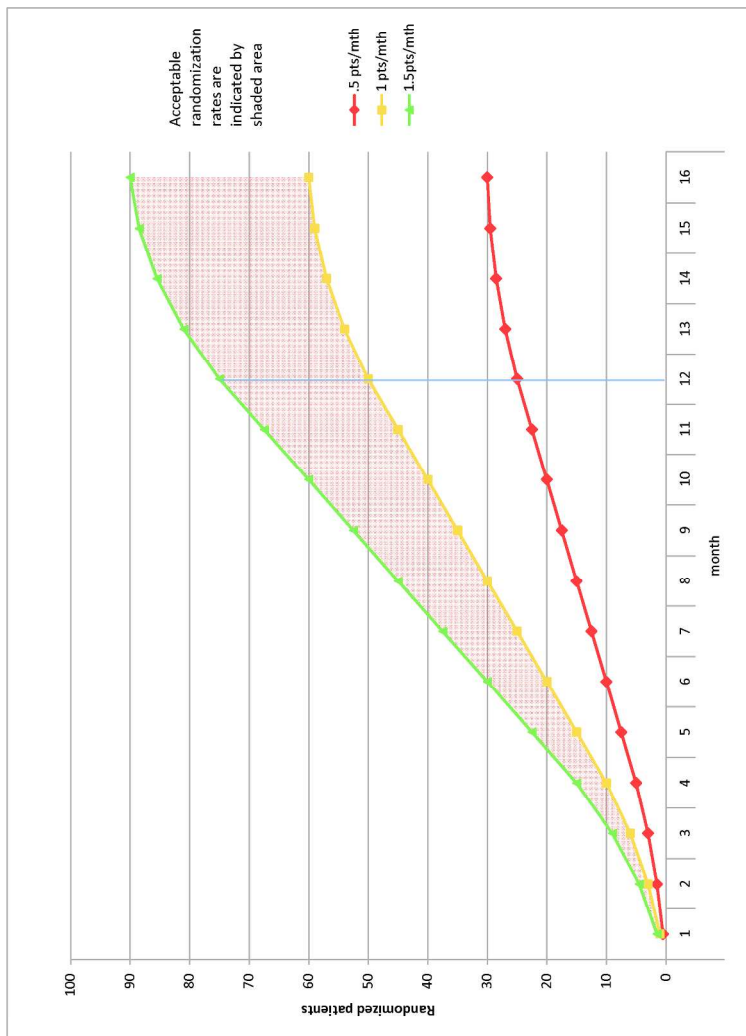


Figure 2: Effect of Recruitment Rate on Study Duration: projects 5 sites with staggered initiation of enrollment

Figure 2  
215x279mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

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

Section/item	Item No	Description	Addressed on line number
<b>Administrative information</b>			
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 ___



1  
2  
3 **Introduction**  
4

5 Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	___ 88-122 ___
6 rationale		studies (published and unpublished) examining benefits and harms for each intervention	
7			
8	6b	Explanation for choice of comparators	___ 111-119 ___
9			
10 Objectives	7	Specific objectives or hypotheses	___ 119-121,131-137 ___
11			
12 Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
13		allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___ 115, 125-130 ___
14			

15  
16 **Methods: Participants, interventions, and outcomes**  
17

18 Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	___ 128 ___
19		be collected. Reference to where list of study sites can be obtained	
20			
21 Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	___ 142-158 ___
22		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
23			
24 Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	___ 192-207 ___
25		administered	
26			
27	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	___ 265-268 ___
28		change in response to harms, participant request, or improving/worsening disease)	
29			
30	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	___ 243-301 ___
31		(eg, drug tablet return, laboratory tests)	
32			
33	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___ 306-308 ___
34			
35 Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	___ 241-301 ___
36		pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
37		median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
38		efficacy and harm outcomes is strongly recommended	
39			
40			
41 Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	___ 347, 624 ___
42		participants. A schematic diagram is highly recommended (see Figure)	
43			
44			
45			

1  
2  
3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including \_\_\_\_\_377-385\_\_\_\_\_

4 clinical and statistical assumptions supporting any sample size calculations  
5  
6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size \_\_\_\_\_169-179\_\_\_\_\_

7  
8 **Methods: Assignment of interventions (for controlled trials)**

9  
10 Allocation:

11  
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any \_\_\_\_\_183-185, 187-191\_\_\_\_\_

13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
15 or assign interventions  
16  
17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, \_\_\_\_\_183-185, 188-191\_\_\_\_\_

18  
19  
20  
21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to \_\_\_\_\_180-191\_\_\_\_\_

22  
23 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome \_\_\_\_\_129-130,285,444-446\_\_\_\_\_

24  
25  
26  
27  
28 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's \_\_\_\_\_n/a\_\_\_\_\_

29 allocated intervention during the trial  
30  
31

32 **Methods: Data collection, management, and analysis**

33  
34 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related \_\_\_\_\_302-330\_\_\_\_\_

35 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
36 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
37 Reference to where data collection forms can be found, if not in the protocol  
38  
39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be \_\_\_\_\_282-301\_\_\_\_\_

40 collected for participants who discontinue or deviate from intervention protocols  
41  
42  
43  
44  
45

1				
2				
3	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
4				
5				
6				
7	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__
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__n/a__
11				
12		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__
13				
14				
15				
16	<b>Methods: Monitoring</b>			
17				
18	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__
19				
20				
21				
22				
23		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__
24				
25				
26	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__
27				
28				
29	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__
30				
31				
32				
33	<b>Ethics and dissemination</b>			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__362-63,180-183__
36				
37				
38	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__
39				
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

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_____
<b>Appendices</b>			
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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.