Aneurysmal Subarachnoid Hemorrhage - Red Blood Cell Transfusion and Outcome (SAHaRA):
A Randomized Controlled Trial

Sponsor	Ottawa Hospital Research Institute
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Abbreviated Title: SAHaRA Study

Sponsor: Ottawa Hospital Research Institute

Protocol Date: September 03, 2020, v3.0

I have read this clinical trial protocol and agree to conduct the trial in accordance with the approved protocol, standard operating procedures (SOPs), applicable laws and regulations and the ICH/GCP guidelines for good clinical practice.

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3 Abstract

Background: Aneurysmal subarachnoid hemorrhage (aSAH) is an important disease with devastating outcomes. Morbidity can be profound, with less than one third of survivors achieving a full functional recovery. Anemia is common in these patients and is a potential critical factor affecting secondary injury, an often protracted process. Despite physiologic evidence and management guidelines that support maintaining a higher hemoglobin level in patients with aSAH, current stated practice from surveys and from our multi-center cohort study suggests a more restrictive approach to transfusion in a similar fashion to other critical care patients. The clinical importance of varied transfusion thresholds in aSAH has never been studied in a large and rigorous randomized trial. In our internal pilot RCT we have demonstrated the feasibility of patient enrolment and trial conduct. In collaboration with the Canadian Critical Care Trials Group, we aim to conduct an open-label single blind RCT in adult patients with aSAH to examine the effect of a liberal compared to restrictive RBC transfusion strategy (Hb trigger ≤100g/L vs ≤80g/L respectively) on 12 month functional neurologic outcome.

Objectives: Primary: To determine if a liberal compared to restrictive RBC transfusion strategy (Hb trigger ≤100g/L vs ≤80g/L respectively) in adult patients suffering from acute aSAH and anemia (Hb≤100g/L) decreases the combined rate of death and severe disability at 12 months.
Secondary: To evaluate the effect of a liberal versus a restrictive (Hb trigger ≤100g/L vs ≤80g/L) RBC transfusion strategy in acute aSAH patients with anemia (Hb≤100g/L) on: a) 12-month overall function and quality of life; b) mortality and c) delayed cerebral infarcts on routine follow-up CT scans.

Methods:
Design/Setting: Multicenter pragmatic, open-label blinded-endpoint randomized control trial.
Participants: Adult aSAH patients within 10 days of their initial bleed and anemia (Hb of ≤ 100 g/L) will be eligible for enrolment.
Randomization: Web-based central computer-generated randomization, stratified by centre, will be undertaken from the host centre.
Intervention: Patients will be randomly assigned to either a liberal (Hb≤100g/L) or a restrictive (Hb≤80g/L) transfusion trigger strategy for the first 21 days.
Outcome: Primary: 12 month modified Rankin Scale score.
Secondary: a) Functional Independence Measure (FIM) and the EuroQOL Quality of Life Scale (EQ5D) at 12 months, b) number of RBC units transfused, c) lowest daily hemoglobin, d) transfusion-related complications, e) incidence and severity of delayed cerebral ischemia, f) incidence of cerebral infarction, g) need for and duration of mechanical ventilation, h) ICU and hospital lengths of stay, and i) mortality.
Sample Size: To demonstrate a 10% absolute reduction (40% to 30%, 25% relative improvement) in our primary outcome in the intervention group, a sample size of 740 patients is necessary assuming 80% power, a type I error of 5% and a conservative 3% adjustment for loss to follow-up.
Analysis: Our primary outcome will be examined by Mantel-Haenszel chi-square statistics and presented as the absolute risk reduction.

Significance: The SAHaRA trial will clarify the role of treating anemia with RBC transfusion in this unique and vulnerable patient population, and determine whether that impacts on functional outcomes and mortality. It will guide best practice standards and clarify the optimal RBC transfusion strategy in patients with aSAH.

4 Project Summary

Title	Aneurysmal Subarachnoid Hemorrhage - Red Blood Cell Transfusion and Outcome (SAHaRA); A Randomized Clinical Trial
Hypothesis	We hypothesize that in adult patients suffering from aSAH and anemia, a liberal RBC transfusion strategy as compared to a restrictive RBC transfusion strategy decreases the combined rate of death and severe disability at 12 months (using the modified Rankin Scale)
Design	Multicenter pragmatic, prospective randomized open-label blinded-endpoint controlled trial
Sponsor	Ottawa Hospital Research Institute
Funding	Canadian Institutes of Health Research: FRN - PJT153247
Sample Size	To demonstrate a 10% absolute reduction (40% to 30%, 25% relative improvement) in our primary outcome in the intervention group, a sample size of 740 patients is necessary assuming 80% power, a type I error of 5% and a conservative 3% adjustment for loss to follow-up
Primary outcome	Modified Rankin Scale (mRS) score at 12 months
Secondary outcomes	Functional Independence Measure (FIM) and the EuroQOL Quality of Life Scale (EQ5D) at 12 months. Cerebral infarction related to Delayed Cerebral Ischemia (DCI) or to complications from securing the ruptured aneurysm, need for and duration of mechanical ventilation, length of stay and mortality in ICU and hospital
Inclusion Criteria	1. Age ≥18 years old at time of SAH 2. First ever episode of aneurysmal SAH 3. Diagnosis of aSAH as confirmed by treating physician (eg: neurosurgeon or neuro-interventionalist) and supported by blood in subarachnoid space (e.g. cranial imaging or CSF positive for xanthochromia, surgical visualization) that is the result of a ruptured aneurysm (e.g. direct visualization, cranial imaging or catheter angiogram) 4. Hb ≤100g/L within 10 days following aSAH (defined by first day of hospital presentation)
Exclusion Criteria	1. Physician and or family decision to withdraw/withhold active medical care at time of enrolment 2. Active bleeding with hemodynamic instability at time of enrolment 3. Patients with contraindication or known objection to blood transfusions 4. SAH due to mycotic aneurysm, infundibulum and vascular malformations.
Intervention	Eligible patients will by randomized to either a restrictive or a liberal RBC transfusion strategy. For patients randomized to the restrictive group, an RBC transfusion is permitted once a hemoglobin level of ≤80g/L is observed over the first 21 days following aSAH. Patients randomized to the liberal group will receive an RBC transfusion triggered by a hemoglobin level of ≤100g/L over the first 21 days in hospital following aSAH.

5 Clinical Problem and existing knowledge gaps

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating illness caused by the spontaneous rupture of an enlarged, weakened artery in the brain. It affects a young population and is a significant cause of premature death and loss of potential life years, similar in magnitude to ischemic stroke[1]. It is a common neurologic reason for intensive care unit (ICU) admission[2] and is associated with a mortality rate of 35% in North America (range 20-67%)[3]. Less than one third of afflicted patients make a full recovery[4] and 20% of survivors experience significant morbidity[5] and impacts on daily living.

Anemia (hemoglobin [Hb] <100g/L), which affects more than 50% of aSAH patients, is associated with worse clinical outcomes and is a critical factor affecting secondary injury.[6–10] Preclinical studies in brain injury suggest that red blood cell (RBC) transfusions to treat anemia improves oxygen delivery.[4] However, RBC transfusions are not without risk and are a limited and expensive resource.[11] Therefore, the rationale for transfusion in aSAH must be supported with strong clinical evidence. We have demonstrated that **the current evidence examining the association between RBC transfusion and aSAH outcome is limited to a few observational studies with conflicting results and significant methodological limitations**.[5,6,8,9,12–16] To date, only one small trial (N=44) has compared two transfusion targets (100g/L and 115g/L) in aSAH, but was clearly underpowered to examine clinically important outcomes.[17] Despite this absence of evidence, current aSAH management guidelines recommend considering RBC transfusion in anemic patients *at risk* for cerebral ischemia, but do not suggest specific transfusion thresholds to guide clinicians.[18,19] These recommendations are in contrast with current stated aSAH practice management from surveys[20] and evidence from clinical trials in other critically ill adult and pediatric populations which support a more restrictive RBC transfusion approach.[21,22] Data from our Canadian multicenter retrospective observational study also suggests that critical care clinicians use a more restrictive approach to transfusion (lower hemoglobin) in aSAH; similar to other critical care patients.[23] **Unlike other critically ill patients, the brain injury and the sequelae that follow (e.g. DCI) may make aSAH patients more susceptible to the decreased oxygen delivery associated with anemia.** Considering this paradox, there is a pressing need to generate high-quality evidence to guide clinical RBC transfusion practices in aSAH. The clinical impact of varied transfusion thresholds in aSAH has never been studied in a large and rigorous randomized trial. The urgent need for quality evidence to guide transfusion practice in aSAH has been identified by influential societies, editorials and practice guidelines.[14,18,19,24] In collaboration with the *Canadian Critical Care Trials Group* (www.ccctg.ca), we propose the largest multicenter RCT ever conducted comparing 2 RBC transfusion strategies in patients with aSAH to evaluate their impact on relevant clinical outcomes.

5.1 Hypothesis to be tested

Our overarching hypothesis is the following: *In adult patients suffering from aSAH and anemia, a liberal RBC transfusion strategy as compared to a restrictive RBC transfusion strategy **decreases** the combined rate of death and severe disability at 12 months (using the modified Rankin Scale [mRS]).*

5.2 Study Objectives

Our primary objective is to evaluate the effect of a liberal (Hb trigger ≤100g/L) versus a restrictive (Hb trigger ≤80g/L) RBC transfusion strategy in acute aSAH patients with anemia (Hb≤100g/L) on patient-oriented functional neurologic outcome at 12 months.

Our secondary objectives are to evaluate the effect of the liberal versus the restrictive RBC transfusion strategy on: a) 12-month overall function; b) quality of life at 12 months; c) mortality and d) clinically relevant stroke at hospital discharge on routine cranial computed tomography (CT) imaging.

5.3 Prior Work by Investigative Team in Preparation for this Trial

The Aneurysmal SubArachnoid Hemorrhage–Red Blood Cell Transfusion And Outcome (SAHaRA) Randomized Controlled Trial represents the culmination of a large program of research (Figure 1). The principal and SAHaRA investigators have completed extensive background work, preliminary and pilot data gathering as well as study capacity building in anticipation of the SAHaRA trial.

Background Work: We have completed a systematic review of comparative studies of RBC transfusion thresholds in neurocritically ill patients published in *Critical Care* in 2012.[25] We identified only 1 study in aSAH patients. We extended the systematic review to include observational studies and the grey literature and found a total of 15 relevant full publications (highlighted in the study proposal). All but 1 are non-randomized studies examining RBC transfusion in aSAH patients, and demonstrate conflicting results at best. These studies are limited by potential selection bias, misclassification bias, confounding due to indication and residual confounding. The only RCT is small with 44 patients and lacked the power to test meaningful clinical outcomes. We have demonstrated that there is insufficient evidence to support the use of a specific transfusion strategy in the aSAH patient population.

Preliminary Data:

1 Aneurysmal SAH Epidemiologic Study: The principal investigator (SE) examined the use of administrative databases to identify primary SAH patients and described hospital incidence and case-fatality rates. This project identified a complete cohort of patients with aSAH and created a prediction model for identifying aSAH patients retrospectively for future planned cohort studies. (Manuscripts published[26,27])

2 Single-center retrospective pilot cohort study: We conducted a retrospective cohort study of aSAH patients at The Ottawa Hospital admitted from 2007-2008 to pilot data collection and to create, test, refine and examine feasibility related to data collection points on transfusion practices. (Presented at Canadian Critical Care Forum, Fall 2013)

3 SAHaRA Canadian multicenter observational study: We conducted a multicenter retrospective cohort study of aSAH patients (n=527) admitted to any of 4 academic centers across Canada between 1 January 2012 and 31 December 2013. The primary objective was to describe a Canadian aSAH population with respect to both anemia incidence and RBC transfusion practices.[23,28] Anemia (hemoglobin ≤ 100g/L) prevalence was 51.8% and the median pre-transfusion hemoglobin in the 19% of the cohort transfused was 79g/L (IQR: 74-93). (Supported by peer-reviewed grants from Depts of Medicine/Critical Care, uOttawa, presented at an international conference[23,28])

CIHR/CBS-funded pilot RCT (NCT02483351): We have successfully completed enrolment into the SAHaRA internal pilot RCT, the principal (SE) and SAHaRA investigators, in collaboration with the CCCTG, have demonstrated successful recruitment, adherence to intervention, and trial protocol feasibility. There have been 2 interim analyses and DSMB reviews which supported continuation without modification (60 of 60 patients), we demonstrated a recruitment rate of >1 patients/center/month. Adherence to treatment allocation was 92% (15 deviations and 3 violations from 97 transfusion episodes). The difference of mean pre-transfusion hemoglobin between groups was 21.1±6.5 g/L. RBC transfusion occurred within 6 hours of trigger hemoglobin in 84.5% of transfusions and within 11 hours in 100%. We have created the necessary infrastructure, procedures and network to successfully conduct the full trial. (Funded CIHR/CBS-201507-SE-343843; Protocol manuscript published[29])

With this above work, the network-building and partner collaborations we have established, we are perfectly positioned to complete the SAHaRA trial.

6 Approach and Methods

6.1 Trial design

We propose a multicenter pragmatic randomized trial in patients with aSAH that will compare the effect of a liberal to a restrictive RBC transfusion strategy on the combined rate of death and severe disability at 12 months (Figure 1B). Our PROBE (open-label, blinded endpoint) approach has been informed by and tested in our CIHR/CBS-funded pilot RCT.

Study Design Rationale: A multi-center design is essential for the results to be widely generalizable.
Like other RBC transfusion threshold trials[22,30–32], an open-label design is necessary given the inability to blind bedside clinicians to hemoglobin levels. Further, PROBE designs have been used in multiple successful, practice-changing stroke trials[33–35]. A 12-month outcome assessment is essential as shorter assessments will likely bias towards worse outcomes and longer duration of follow-up may threaten participant retention.

6.2 Study Population (inclusion/exclusion criteria)

Inclusion Criteria:

1. Age ≥18 years old at time of SAH
2. First ever episode of aneurysmal SAH
3. Diagnosis of aSAH as confirmed by treating physician (e.g. neurosurgeon or neuro-interventionalist) and supported by blood in subarachnoid space (e.g. cranial imaging or CSF positive for xanthochromia, surgical visualization) that is the result of a ruptured aneurysm (e.g. direct visualization, cranial imaging or catheter angiogram)
4. Hb ≤100g/L within 10 days following aSAH (defined by first day of hospital presentation)

Similar criteria have been used in previous studies involving aSAH patients and in our pilot RCT.[9,36,37]

Exclusion Criteria:

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

6.3 Trial interventions

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

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

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

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

6.4 Justification of the two triggers

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

a) In a survey of 531 practicing intensivists, neurointensivists and neurosurgeons the median transfusion hemoglobin trigger ranged from 75 to 80g/L depending on SAH grade.[38]
b) Amongst practicing intensivists, neurointensivists and neurosurgeons the lowest acceptable threshold hemoglobin to trigger a RBC transfusion was 70g/L in >70% of respondents.[38]
c) A Canadian multicenter observational study (N=527) 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).[23]

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

a) Physiologic evidence that RBC transfusion increases oxygen delivery and cerebral tissue oxygen tension.[39–41]
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.[39]
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.[42]

d) A hemoglobin level of <100g/L was associated with brain tissue hypoxia and metabolic distress compared to those with hemoglobin >100g/L.[43]
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. [38]
f) A transfusion trigger of 100g/L has previously been shown to be safe in an aSAH population.[17]

6.5 Duration of the intervention

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

6.6 Patient-oriented outcome measures

Primary outcome: Our primary outcome is the modified Rankin Scale (mRS) score at 12 months. The mRS, a 7-point ordinal scale, is used as the outcome measure over mortality as it includes a spectrum allowing consideration of severe disability and mortality together since both are highly clinically significant and patient relevant. Neurologic outcome as assessed by mRS is the most prevalent outcome measure in stroke literature including aSAH literature[8,17,44–48] and is readily interpretable by this community. It takes <15 minutes to administer, and can be completed using a structured[49–51] and/or telephone[52] interview.
Secondary outcomes: Our secondary outcome measures include the Functional Independence Measure (FIM) and the EuroQOL Quality of Life Scale (EQ5D) at 12 months. They are specifically chosen as they complete the different aspects of the 3 primary levels of body function and stroke rehabilitation (impairment, activity and participation).[51] They are explicitly validated and recommended outcome measures in stroke research.[52] The FIM is a validated tool[53,54] consisting of 18 items that assesses 13 different motor and 5 cognitive tasks previously tested in stroke populations including aSAH[53,55], and has an established minimal clinical important difference (MCID) in this population[56]. It has demonstrated excellent consistency in inter-rater reliability and internal consistency specifically in neurologic disorder populations. It is easy to administer and is validated for use by telephone and via proxy respondents[51]. The EQ5D is a short and simple 2-part questionnaire that may be self-administered, completed by interview or via a proxy respondent, and is used to value and describe health states[51]. We will also capture the number of RBC units transfused, lowest daily hemoglobin, complications related to transfusion**,** incidence and severity of delayed cerebral ischemia (DCI) including radiographic vasospasm. We define DCI as a neurologic deterioration, an otherwise unexplained decrease in Glasgow Coma Scale score of ≥2 points or new focal neurological deficit for ≥1 hour[59]. We have defined, a priori, radiographic vasospasm as a reduction of cerebral artery diameter on digital subtraction angiography (classified as mild [0-33% reduction], moderate [34-66% reduction] or severe [67-100% reduction]) or by transcranial Doppler of the middle or anterior cerebral artery (classified as mild [mean flow velocity of ≥120 and <160 cm/sec AND Lindegaard ratio ≥3], moderate [mean flow velocity of ≥160 and <200 cm/sec AND Lindegaard ratio ≥3] or severe [mean flow velocity of ≥200 cm/sec AND Lindegaard ratio ≥3]).[57–59] We will finally capture the incidence of cerebral infarction on routine CT head imaging (related to DCI or to complications from securing the ruptured aneurysm), need for and duration of mechanical ventilation, length of stay and mortality in ICU and hospital.

The three outcome measurement instruments (mRS, FIM and EQ5D) will be implemented by trained and qualified study staff, at the coordinating center, blinded to the intervention according to a defined schedule. Vital status at discharge, adverse events and other secondary measures will be captured using a case report form prospectively by the site PI and/or RC.

6.7 Proposed frequency and duration of follow up

Our primary outcome measure (mRS) will occur at 12 months. Blinded outcome assessment will be completed at 6 (mRS) and 12 months (mRS, FIM and EQ5D).

6.8 Sample Size

Based on our foundation work and previously published literature, we anticipate poor neurologic outcome (mRS score of ≥4) at 12 months in 40% of the restrictive arm group.[18,28,63,64] Previous studies involving SAH patient populations have supported a minimal clinically important difference (MCID) of a 25% relative improvement in poor neurologic outcome.[65] Therefore, to demonstrate a 25% relative improvement in event rate (i.e. from 40% to 30%), a total sample size of 740 patients (test of independent proportions[66]) is necessary given 80% power, a type I error of 5% and a conservative 3% loss to follow-up factor.

6.9 Criteria for Removal from Study

Criteria for removal from the study are described in this section:

- Participant is unable to tolerate the study intervention
- Participant is unable to complete all required study procedures
- New information shows that the study intervention is no longer in participants best interest
- The site investigator no longer feels this is the best option for participant
- The Sponsor decides to stop the study
- The research ethics board (REB) withdraws permission for this study to continue

6.10 Analytic Plan

Baseline characteristics and management data will be presented as means (continuous measures) or proportions (categorical or ordinal data) with 95% confidence intervals or interquartile ranges (IQR). An independent Methods Center statistician, external to the study team, will conduct all analyses by the intention-to-treat principle.

Primary Outcome: Our primary outcome is poor neurologic outcome at 1 year and will be presented in terms of relative risk with 95% confidence intervals. We define poor neurologic outcome as mRS ≥4. As a secondary analysis, we will report absolute risk reduction using a proportional odds approach which is more sensitive for detecting a shift over the entire spectrum of outcome (mRS 7-point ordinal scale), and thus increases the statistical power.[48,67,68] We will also conduct adjusted analyses for age, sex, SAH severity (using WFNS grade), clip vs coil and DCI using the generalized linear model.

Secondary Outcomes: Our secondary outcomes (see 5.6) will be assessed using multivariable linear or logistic regression models for continuous and dichotomous outcomes respectively. We will adjust for the same characteristics as in the primary outcome.

6.11 Proposed frequency of analyses

We plan one full interim, blinded analysis after the first 370 patients randomized to be reviewed by the Data Safety Monitoring Board (DSMB) guided by a pre-specified charter. Regular (biannual) reports of patient recruitment and adverse event reporting will be provided to the DSMB.

6.12 Planned subgroup analyses

A priori subgroup analyses include patient age, sex and those with associated intraventricular hemorrhage and DCI at time of enrolment.

7 Safety Reporting

7.1 Adverse Event Monitoring and Source Documentation

All recipients are to be assessed for adverse events according to local institutional practice, except where additional assessment is required per protocol. Source documentation of reportable adverse events should be according to institutional practice, except in cases where additional information is required to be documented by the protocol.

7.2 Adverse Event Reporting

7.2.1 Expected Serious Adverse Events (eSAE)

Have been defined a priori and are being collected and reported as study outcomes and as such will not be labeled nor reported a second time as serious adverse events.[68]

7.2.2 Unexpected Serious Adverse Events (uSAE)

All uSAEs are to be brought to the attention of the site PI (following site specific standard operating procedures). Causality (see section 7.3.4) of the uSAE should be adjudicated by the site PI. All possibly or related uSAEs are to be reported in the Data Collection Forms (both study arms) as described in this section:

A. Monitoring and reporting should begin on the first day of study intervention and continue until either:
    a. the uSAE has been resolved
    b. day 28 (post-ictal bleed), death or discharge whichever occurs first
        i. if the uSAE remains ongoing at day 28 it will be reported as such
B. Supporting source documentation of all reported uSAEs must be submitted for additional and final central adjudication.
C. Abnormal laboratory results do not need to be recorded unless considered by the investigator to be relevant in terms of subject or trial safety (or in relation to a serious adverse event that is being reported).

7.2.3 Serious Adverse Event Reporting

All reportable unexpected SAEs (see 7.2.2 and definition section 7.3.3) must be reported to the Coordinating Center **within 72 hours** of the site's knowledge of the unexpected SAE. The Study Chair and/or Study Steering Committee will review all unexpected SAE's received from the sites. If an unexpected SAE is confirmed, a document summarizing the SAE will be distributed to participating sites. Sites should follow the guidelines of their local REB with respect to the submission of SAEs that occur at the site as well as SAE Notifications

7.3 Definitions

7.3.1 Adverse Event (AE)

The International Conference on Harmonization (ICH) definition of an adverse event is: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

7.3.2 Serious Adverse Event (SAE)

In reference to the ICH and Health Canada definition of a Serious Adverse Event, we will define as any untoward medical occurrence that either:

- Results in death
- Is life-threatening
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Results in a congenital anomaly/birth defect.

7.3.3 Unexpected Adverse Event (uAE)

In accordance with the ICH Guidelines: An unexpected adverse event is one in which the nature or severity is not consistent with the applicable product information; in this instance, the red blood cell transfusion trigger protocol. For example, death from transfusion would be an unexpected serious adverse event as opposed to death from sepsis.

A subset of uAE's will meet SAE criteria (section 7.3.2), this subset, being both unexpected and serious, will be reported as uSAE's as described in section 7.2.3.

7.3.4 Causality

Investigators are required to assess the relationship, if any, of each AE (that meets the criteria for reporting) to the red cell transfusion(s) trigger strategy. Clinical judgment is to be used to determine the degree of certainty with which an AE can be attributed to the intervention. Causality criteria are defined as follows:

- **Not related:** There is not a reasonable possibility that the adverse event may have been caused by the study intervention.
- **Possibly related:** The AE may have been caused by the study intervention; however there is insufficient information to determine the likelihood of this possibility
- **Related:** There is a reasonable possibility that the AE may have been caused by the study intervention.

8 Trial Management

8.1 Participant enrolment, consent, randomization and allocation concealment

Local research coordinators will screen each patient admitted for aSAH to either the Intensive Care Unit or Intermediate Care Unit for up to 10 days after the qualifying bleed (Figure 1B). Enrolment up to 10 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[36]. Further, our SAHaRA observational study demonstrated that 87% of incident anemia occurred within the first 10 days, and that 97% did so while admitted to a high-acuity unit.[28] The risk of new onset DCI, a significant threat to morbidity and mortality in this population occurs most frequently within 7-10 days but its duration may surpass this period.[18] In our pilot RCT, the median day of randomization was 3 days (IQR 2-5 days).

As in our pilot RCT, patients meeting eligibility criteria (or their substitute decision maker (SDM) in the event the patient is unable to provide informed consent) will be approached for informed consent, using a mixed consent model and in accordance with Good Clinical Practice as well as standard local procedures as approved by each local REB. As in the pilot RCT, we will use a deferred informed consent approach due to the time-sensitive nature of the intervention whose potential benefit lies in timely administration. Substitute decision makers are not always immediately available, or the timeliness of the approach may be inappropriate, such that it may be impractical to explain the study, obtain informed consent and initiate the intervention in a timely manner.

The same web based randomization system maintained at the Coordinating Center will be used to allocate treatment assignments. Under the guidance of the site principal investigator (SI) or research coordinator (RC), the participant's eligibility criteria will again be confirmed with a checklist using a web interface.

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

8.2 Baseline Characteristics and Co-Interventions

The study team will capture important baseline characteristics (e.g. age, sex, ethnicity, language, comorbidities, aneurysm and SAH characteristics/grade) at time of enrolment for comparison between the 2 study groups. In this pragmatic trial, patient management outside of RBC transfusion will be left to the discretion of the treating team and in accordance with practice guidelines[18] which will be made available to all participating centers and clinicians. Potentially confounding cointerventions (e.g.: nimodipine use, aneurysm securing technique, blood pressure and DCI management) will be carefully documented daily in the case report form by the site research coordinators.

8.3 Study Centers

From the pilot RCT, 5 centers have already committed to the trial with REB approval and executed contracts. We have demonstrated the ability to enroll into the trial with a mean randomization rate of > 1 patient/center/month recruiting. Eight additional centers have agreed to participate in the full trial including Kingston General Hospital (Kingston), Royal Alexandra Hospital (Edmonton), Centre Hospitalier de l'Université de Montréal (Montréal), Centre Hospitalier Universitaire de Sherbrooke (Sherbrooke), London Health Sciences Center, Sunnybrook Health Sciences Center, Toronto Western Hospital, and Manitoba Health Sciences Center (Winnipeg) (see supporting letters). Future additional centers for the full trial have been identified through our CCCTG partners and will be onboarded as required to meet the proposed recruitment timelines of this study, some of these centers may be international.

8.4 Day to day management of the trial

The trial will be coordinated from the Ottawa Hospital Research Institute (OHRI – Study sponsor). The Trial Coordinator will be responsible for the day-to-day proceedings of the trial including collecting, validating and collating reported data from study sites and liaising with the statistician. The trial statistician will be based out of the Methods Center of the OHRI. The RCs of the participating sites will carry out patient screening, recruitment, consent, case report filing, data collection, storage and dissemination to the coordinating center. Site co-investigators will act as leadership, educators, recruiters and resources for the day-to-day proceedings and financing. We have established policies and procedures including an electronic web-based randomization and case-report form as utilized in the pilot RCT.

9 Potential Challenges and mitigation strategies

9.1 Study recruitment and compliance

Recruitment Strategies: Prior to Trial Start-up: We will hold a start-up meeting with the participating sites in conjunction with a Canadian Critical Care Trials Group Scientific Meeting. Education sessions at the participating sites for physicians (neurologists, neurosurgeons, neuroradiologists and intensivists), resident staff and bedside nurses will take place in the form of rounds, mini-sessions and morning teaching to inform on the need for this study, study rationale and participant inclusion criteria. During the Trial: Logs of screened patients including details of ineligibility and logs of participant refusals (either by treating physician, patient or substitute decision maker) will be sent monthly to the coordinating center for analysis and to review strategies to increase enrolment. Quarterly updates on recruitment efforts will be disseminated to all participating centers along with recruitment reminders.

Recruitment Rate: The SAHaRA pilot RCT has demonstrated the ability to successfully recruit patients into this trial applying the same eligibility criteria. With a goal of >1patient/center/month, we have demonstrated feasibility in recruiting. Like the 5 pilot sites, the proposed trial centers are all tertiary care centers with active neurovascular programs. Once all centers are actively enrolling, we anticipate a recruitment duration of 3 years to meet the pre-specified sample size.

Study Compliance: Study compliance will be measured in 2 domains:

1) **Adherence to allocated transfusion threshold**: This will have occurred if: 1) a RBC transfusion is given in response to the transfusion threshold being crossed; or 2) a repeated hemoglobin value no longer crosses the threshold ending the transfusion threshold event. **Non-adherence** will be considered to have occurred if a) an RBC transfusion occurs before a transfusion threshold is crossed; or b) in the liberal arm, a transfusion is not given following a threshold crossing. Non-adherence will be considered a *deviation* if: 1) the early transfusion occurs within 5 g/L above the allocated threshold (e.g. ≤105 g/L for the liberal arm or ≤85 g/L for the restrictive arm) or, 2) in the liberal arm, an RBC transfusion does not occur for a hemoglobin measure up to 5 g/L below the threshold (i.e.: a transfusion does not occur for a Hb of 95-100 g/L). All other threshold event non-adherences will be considered a protocol violation. Details on non-adherence (date and hemoglobin level prior to transfusion) and reasons for non-adherence will be recorded. In the Pilot RCT we had 93% compliance with RBC transfusion according to allocation at the mid-point interim analysis. In the event of an active blood loss associated with hemodynamic instability, as defined by the treating team, standard resuscitation practices

prevail (including blood product administration). Transfusion under this circumstance would not be a protocol violation. The allocated transfusion strategy will resume when hemodynamic stability is achieved and it is the opinion of the treating team that active bleeding has stopped. Transfusion outside of hemoglobin thresholds for symptomatic anemia will be recorded, but not considered a protocol violation.
2) **Adherence to transfusion protocol (timely transfusion):** As in the pilot, we endeavor not to exceed 6 hours from transfusion threshold event to transfusion initiation, in keeping with revascularization time performance measures in stroke literature[70,71]. Transfusion protocol adherence is thus defined as an RBC transfusion initiated within 6 hours of threshold crossing, or Randomization. Non-adherence will be considered to have occurred if there is a delay of more than six hours between transfusion threshold event and transfusion initiation. Transfusions occurring more than 6 hours but within 24 hours will be considered a protocol deviation. A violation is a transfusion initiated greater than 24 hours from the threshold event. We will document reasons for non-adherence in the study case report form.

To improve protocol compliance and awareness we have involved neurosurgeons, interventionists, transfusion medicine and intensivists at each study site. We will provide on-call house staff and clinicians end-of-the-day and start-of-the-weekend reminders about the study, both for future recruitable patients and enrolled patients. Reminders in the form of stickers and flagged pages will mark enrolled patients' medical record. A list of randomized patients will be kept in the transfusion medicine lab to allow for a secondary check of protocol adherence for when RBC transfusion is ordered. We will monitor daily hemoglobin measures to ensure compliance of transfusion within 6-hour target of meeting the threshold.

9.2 Protecting against sources of bias

Allocation of patients is concealed to prevent selection and information bias. Given the nature of the intervention (RBC transfusion strategy) and its effect on serum hemoglobin measurements, an open-label design is necessary as it is not possible to blind treating practitioners after randomization. As such, we have incorporated independent central blinded outcome assessment and adjudication for all clinical outcomes. Misclassification bias is minimized by applying strict diagnostic criteria for aSAH in the eligibility criteria. Performance bias will be minimized by stratifying patients according to participating sites to ensure equal randomization across sites. We will also track eligible but non-enrolled patients to describe reasons for non-enrolment according to a taxonomy of reasons listed on a study data form. Further, we have attempted to minimize subjectivity in all of the outcome measures by centralizing and blinding the outcome assessor to the treatment allocation and utilizing validated tools for morbidity measures (mRS, FIM and EQ5D) (see Section 6.6). To further reduce risk of bias (performance, attrition, detection and reporting), for the primary outcome, a validated interview/questionnaire administered over the telephone, electronically or by mail will be performed by the assessor (trained and qualified study personnel) blinded to the intervention and who has had no part in the management of the patients.

9.3 Study Monitoring and Auditing

The Trial Coordinator will review the protocol and Data Collection Forms with the investigator and study staff before study initiation at the site initiation visit or the investigator's meeting. A monitor will visit sites as needed throughout the duration of the study to verify the quality of data and to ensure the standards of Good Clinical Practice are being met. (The monitor may be a member of the Study Steering Committee or delegate.) A monitoring plan has been developed and adhered to for the duration of the study (separate document).

The investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the Data Collection Form entries. No information in these records about the identity of the patients will leave the study center. Monitoring standards require verification of the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of all adverse events and outcomes required as per protocol.

The investigator(s)/institution(s) will permit trial-related monitoring, audits, REB review and regulatory inspections(s), providing direct access to source data/documents.

9.4 Loss to follow-up

Previously published papers involving similar patient populations have documented a <1% loss to follow-up.[72,73] Experience within our own investigative team in traumatic brain injury succeeded in >95% 12-month follow-up employing a similar strategy.[74] Clinical outcome assessments will occur at 6 and 12 months and, where possible, by telephone, electronic or mailed interview in lieu of follow-up visits with either the patient or their substitute decision maker to facilitate complete follow-up. Public records will be utilized when patients meet minimum lost to follow up, a minimum of 3 unsuccessful attempts to contact in a 3 month timeframe.

10 Ethics, Safety and Privacy

10.1 Ethics

The study protocol will be submitted for approval by the designated Clinical Trials Ontario (CTO) - Board of Record and/or at each participating centers REB. The **intervention and control** arm of the trial are part of usual care in many centers, and thus the research risk to participants is low. Safety considerations are addressed within the protocol, and allow for individualized care where needed.

10.2 Risks to the safety of participants involved in the trial

By virtue of design, we expect that patients in the liberal transfusion strategy arm (100g/L) will receive more red cell transfusions compared to the restrictive arm (80g/L). It is possible that a greater risk of complications associated with transfusion exists due to exposure. However, this was not the case in the only existing small RCT in SAH [17] or other large RCTs in critically ill patients or other patient populations.[22,72–74] Further, no specific adverse event trends (including acute reactions and infections) associated with either intervention arm have been noted in our current pilot RCT. Complications associated with transfusion will be monitored for, recorded and reviewed by the DSMB as previously described.

10.2.1 Adverse Event Report

Infrequently *(less than 1%)*	***Rarely*** *(less than 0.1%)*	***Very Rarely*** *(less than 0.001%)*
1. Fever 2. Rash	1. Severe allergic reaction that may be life-threatening 2. Transfusion reaction associated with fevers and with damage to RBCs 3. Injury to the lungs 4. Accumulation of fluid in the lungs 5. Infection	1. HIV (AIDS) 2. Hepatitis C 3. Hepatitis B

10.3 Privacy

Increasingly, medical journals and on-line publishers require that data be stored and made available for secondary review and analysis. For publication purposes participant de-identified study data may be shared for re-analysis.

11 Study Timelines and Milestones

We anticipate a trial duration of 60 months (Table 1). With a run-in start-up period, an enrolment rate of 1.5 patients/center/month, we estimate recruitment to be complete at 40 months. Final follow-up will occur 12 months following leaving 6-8 months for data cleaning, database closure, analysis and result dissemination including publication in major journals.

12 Knowledge Translation (KT) Plan

Integrated KT: Knowledge translation will occur throughout the life of the trial and will begin as study awareness through multidisciplinary presentations at participating centers. We have national reach with bedside clinicians as our study team incorporates critical care, neurosurgical and transfusion medicine specialists at each participating site. Further, the team integrates representatives from key national stakeholder groups including the Heart and Stroke Foundation of Canada (K. Butcher, D. Dowlatshahi), Canadian Blood Services (J. Acker), Canadian Critical Care Trials Group (CCCTG – numerous members), and the Canadian Neurocritical Care Society (President – J. Kutsogiannis). Lastly, the trial protocol will be registered and published in a peer-reviewed indexed journal.
End-of-Grant KT: The post-trial knowledge translation strategy includes submission of abstracts at national and international conferences, publication of studies in high-impact peer-reviewed open source journals, and incorporation of our findings into clinical guidelines with our partners at Canadian Critical Care Society/Canadian Neurocritical Care Society. Through site presentations, as well as our established national partnerships and collaborations with Canadian Blood Services, the Heart and Stroke Foundation of Canada, and the Canadian Critical Care Trials Group, we will ensure the optimal dissemination of the results to facilitate optimal supply, best practice guidance and bedside uptake respectively.

13 Study team and environment - Strengths and Contributions

We have formed an investigative team rich in research, methodological, clinical and content expertise and reflects the multidisciplinary team that manages aSAH patients. Dr. Shane English will lead the study (2 hours/week [hrs/wk]). He is a clinician scientist, with an MSc in epidemiology, and intensivist with specific expertise in neurocritical care having completed a clinical fellowship in Cambridge, England. He is an associate scientist at the Ottawa Hospital Research Institute and CCCTG contributing member. He has led the SAHaRA Research Program from inception, including the pilot RCT. A prolific, diverse and experienced Executive Committee consisting of Drs. McIntyre, Fergusson, Chassé, Turgeon, Lauzier and Griesdale supports him. Together, they will oversee all aspects of the study as well as larger research agenda business and will meet at least quarterly (via teleconference) to discuss trial conduct and any challenges (25 hrs). They will also contribute to the formulation of the analytical plan, data interpretation, and the drafting and revisions of manuscripts (30 hrs). Dr. English will meet biweekly with the trial coordinator to review study progress and report to the Executive.
The Steering Committee will consist of the Executive and study site leads (Drs. Kutsogiannis, Kramer, Zarychanski, Althenayan, Almunder, Scales, Singh, Boyd, Sinclair, Chassé, D'Aragon). The Steering Committee members will be responsible for all aspects of study initiation and conduct at their respective sites (~1 hr/wk). These include timely submissions to research ethics boards and supervision of the research coordinators who will screen, enroll, consent and collect data during the pilot, monitoring of recruitment and monitoring adherence to study protocol, and any operational challenges associated with the trial (approx. 0.5 hrs/wk/center). A minimum of four teleconferences of both the Executive and Steering Committees will be held to ensure the communication of all issues pertaining to the study (min 4 hours).

An impressive expert investigative team supports this study. Many members (Drs. English, McIntyre, Chassé, Griesdale, Fergusson, Kramer, Lauzier, Marshall, Pagliarello, Turgeon, Dowlatshahi, Kutsogiannis, Boyd, Singh, Zarychanski, Scales, Da Costa) hold Master's degrees or higher in Epidemiology, Statistics or related fields. Many practice clinically as either intensivists (Drs. English, McIntyre, Chassé, Griesdale, Kramer, Lauzier, Pagliarello, Turgeon, Kutsogiannis, Zarychanski, Althenayan, Chapman, Scales, Singh, Boyd, D'Aragon), neurosurgeons (Drs. Algrid, Sinclair, Da Costa), neurologists (Drs. Dowlatshahi, Boyd, Butcher), physiatrists (Dr. Marshall) or in hematology/transfusion medicine (Drs. Tinmouth, Zarychanski). Several of our team members have extensive experience leading multicenter RCTs (Drs. English, McIntyre, Fergusson, Tinmouth, Butcher); Neurocritical Care research (Drs. English, McIntyre, Algrid, Chassé, Griesdale, Lauzier, Turgeon, Sinclair, Kramer, Kutsogiannis, Althenayan, Chapman, Scales, Singh, Dowlatshahi, Boyd, D'Aragon, Butcher) and blood transfusion research (Drs. English, McIntyre, Chassé, Fergusson, Turgeon, Tinmouth, Zarychanski, Acker). All members have clinical research portfolios in the field of neuroscience, critical care, rehabilitation and/or

transfusion. The team includes members from key stakeholder groups including Canadian Blood Services (Drs. Tinmouth, Acker), Heart and Stroke Foundation of Canada (Drs. Butcher, Dowlatshahi), Canadian Neurocritical Care Society (Dr. Kutsogiannis) and many are active members of the CCCTG. All are key in the development of the protocol, trial awareness and conduct as well as the knowledge translation activities throughout and following the study.

13.1 Research Environment and Resources

The SAHaRA RCT will be coordinated at the Ottawa Hospital Research Institute (OHRI). This world-class university hospital research institute and its associated method's center (OMC) ensures exceptional clinical, research, infrastructure and administrative support to the SAHaRA Program. As in the pilot RCT, under the direction of Dr. English and the Executive Committee, the OMC located at the Center for Practice-Changing Research, will manage the trial coordination, information, computing, accounting and database services, statistical support and knowledge translation activities throughout the trial. The OMC has a vast collective experience in conducting large national and international trials.[78–80] Further, each participating site is supported by local research infrastructure. SAHaRA will be conducted in collaboration with the CCCTG which further supports the program with community support, patient engagement, high protocol adherence and commitment to timely completions. Each participating center has CCCTG-member investigators or are supported by a CCCTG-member and thus have a long and world-renowned history of conducting rigorous, timely and high impact trials.

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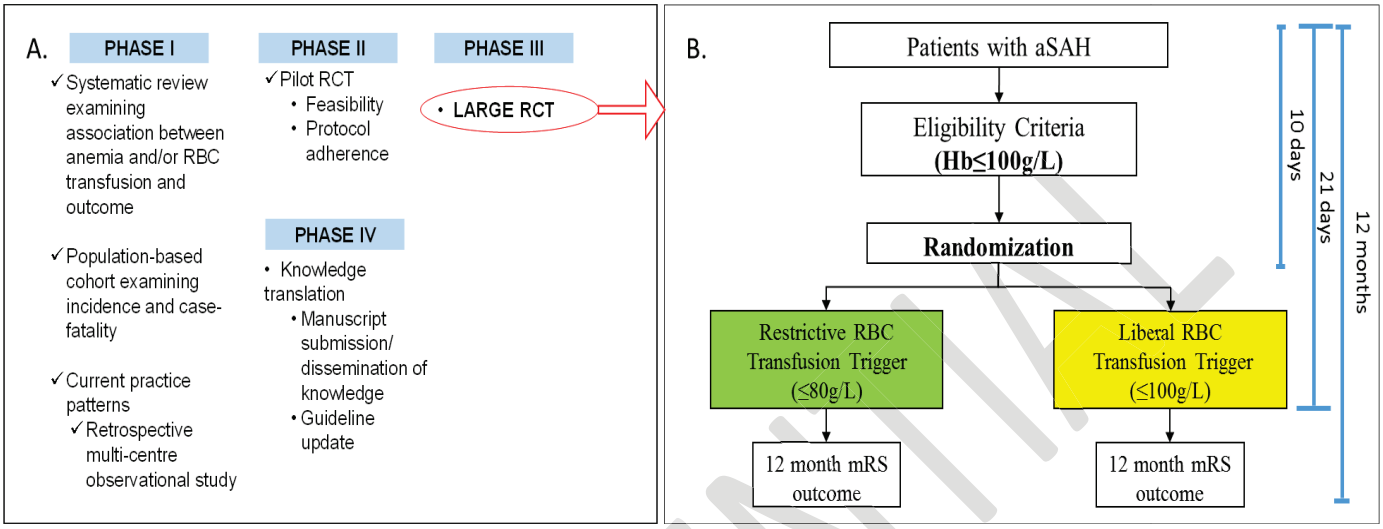
APPENDIX:

Figure 1: The SAHaRA Research Program*:*

A. Current proposed study (circled) in context of research program; B. SAHaRA Trial design



aSAH=aneurysmal subarachnoid hemorrhage, Hb=hemoglobin, mRS=modified Rankin Scale, RBC=red blood cell, RCT=randomized controlled trial

C. SAHaRA Trial outline

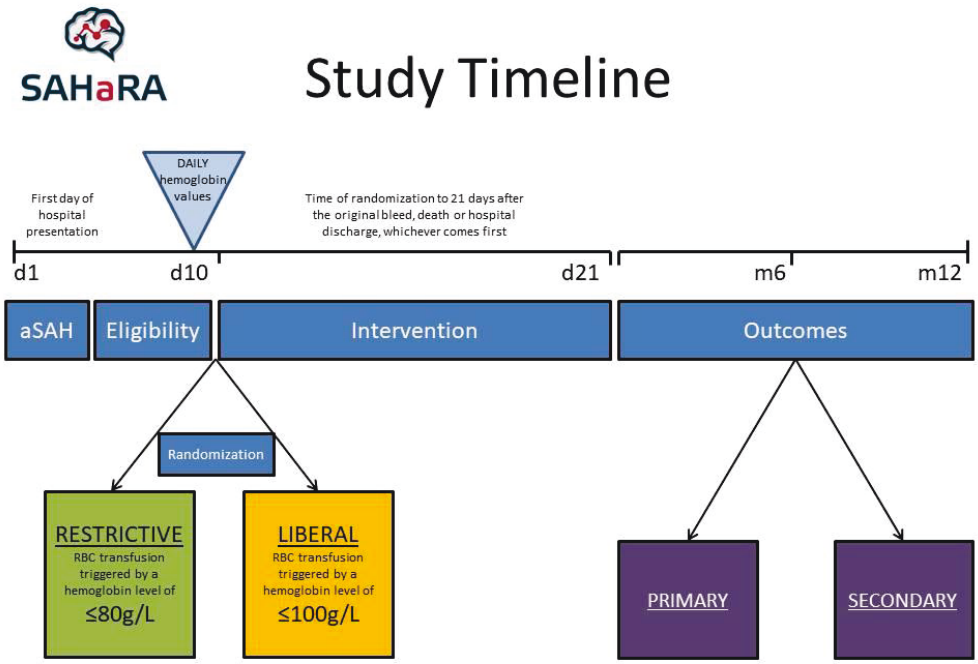


Table 1: Trial timeline, key milestones and deliverables

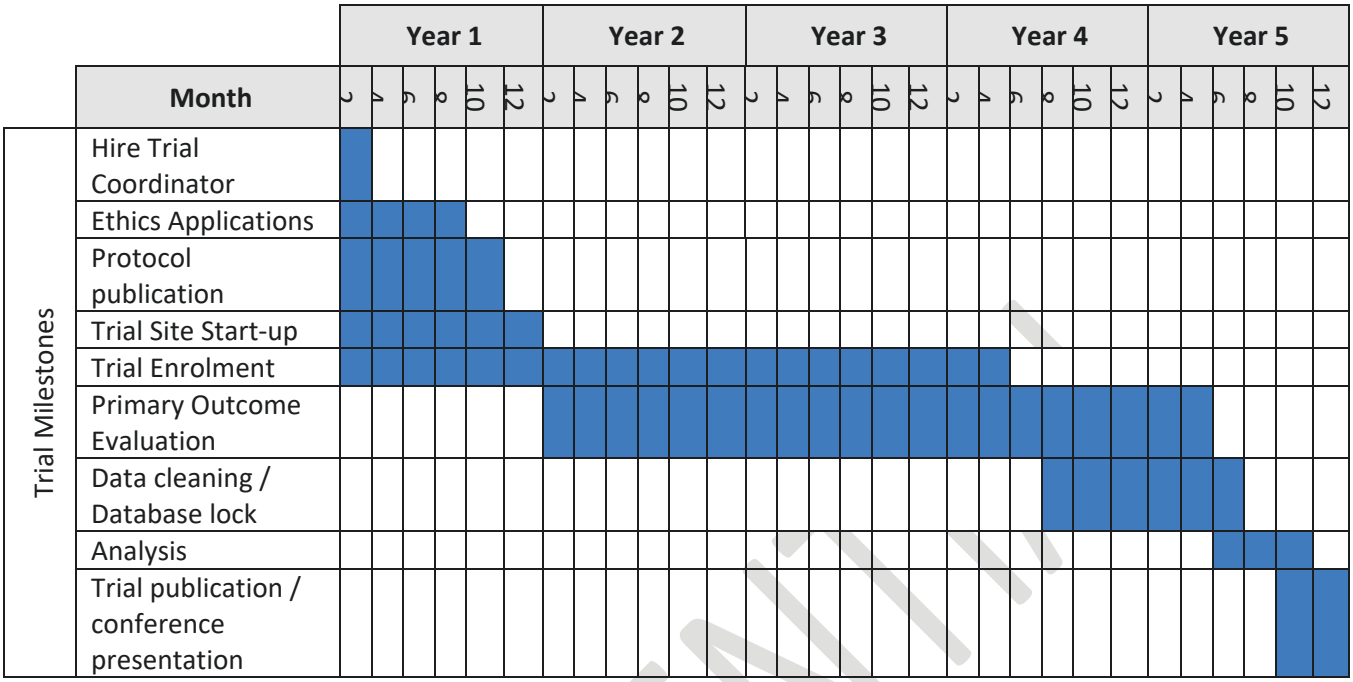


Table 2: Functional outcome measures:

A. Modified Rankin Scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all ADLs
2	Slight disability; unable to carry out previous activities, but able to look after own affairs with assistance
3	Moderate disability; requiring some help but walks without assistance
4	Moderately severe disability; unable to walk unassisted and unable to look after own bodily needs unassisted
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

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

B. Functional Independence Measure**

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

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

Table 3: Important baseline characteristics and co-interventions to be prospectively logged:

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

Factor	**Variable to capture**
Age at enrolment	Age in years
Sex	Male or Female
Ethnicity	As patient identifies
Language	Preferred language
History of CAD, HTN	Present or not
SAH Clinical Severity	WFNS score
SAH radiographic Severity	Modified Fisher Scale Score
Hydrocephalus	Need for EVD
Aneurysm size and location	Size (mm), artery involved
Method aneurysm secured	Clip or coil or not secured
Presence of Delayed Cerebral Ischemia	Delayed cerebral ischemia/radiographic vasospasm *
Presence of cerebral infarct	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 of the middle or anterior cerebral classified as mild (mean flow velocity of ≥120 and <160 cm/sec AND Lindegaard ratio ≥3), moderate (mean flow velocity of ≥160 and <200 cm/sec AND Lindegaard ratio ≥3) or severe (mean flow velocity of ≥200 cm/sec AND Lindegaard ratio ≥3), delayed cerebral ischemia requires a clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of ≥2 points or new focal neurological deficit for ≥2 hours (or ≥1 hour and initiation of therapy))

B. Co-Interventions to be prospectively logged

Co-Intervention		Variable to capture	Operationalization
Delayed Cerebral Ischemia/radiographic vasospasm*	Prophylaxis	Hyperdynamic therapy (prior to diagnosis of DCI)	-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 DCI)	-use of magnesium IV infusion
		Chemical vasodilators (prior to diagnosis of DCI)	-use of infusion of vasodilator (IV) or any IA use (eg: milrinone, paperavine, CCB etc)
	Treatment	Hyperdynamic therapy (after diagnosis of DCI)	-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)		Clip vs coil	
		Time to clip or coil	
Blood pressure management		-daily use of vasopressor	-used or not
		-highest daily target MAP	
Fever/temperature regulation		-fever	-daily highest temperature

MAP=mean arterial pressure, IV=intravenous, IA=intra-arterial, CCB=calcium channel blocker, *radiographic vasospasm defined as a reduction of cerebral artery diameter on digital subtraction angiography and classified as mild (0-33% reduction), moderate (34-66% reduction) or severe (67-100% reduction) or by transcranial Doppler with a mean middle or anterior cerebral artery flow velocity of >200cm/s or an increase of >50cm/s/24h on repeated measures and a Lindegaard ratio of ≥3, delayed cerebral ischemia requires a clinical neurologic deterioration (defined as an otherwise unexplained decrease in Glasgow Coma Scale score of ≥2 points or new focal neurological deficit for ≥2 hours (or ≥1 hour and initiation of therapy))

Table 4: 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, O2 sat, GCS	X	X	X		
Baseline labs	X				
aSAH clinical grade	X				
Neuro imaging (U/S, CT, MRI, Angio...)	X				
DCI monitoring (CTA, U/S, angio...) and management	X	X	X		
Laboratory results		X	X		
Transfusion Requirements		X	X		
Co-intervention Log		X	X		
Adherence to treatment		X	X		
AE Review		X	X		
Neurologic outcome (mRS)			X	X	X
Functional Independence Measure (FIM)					X
EuroQOL Quality of Life Scale (EQ5D)					X