PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Practical Anemia Bundle for Sustained Blood Recovery (PABST-BR) in Critical Illness: A Protocol for a Randomized Controlled Trial
AUTHORS	Warner, Matthew; Go, Ronald; Schulte, Phillip; Beam, W. Brian; Charnin, Jonathan E.; Meade, Laurie; Droege, Kim A.; Anderson, Brenda K.; Johnson, Matthew L.; Karon, Brad; Cheville, Andrea; Gajic, Ognjen; Kor, Daryl

VERSION 1 – REVIEW

REVIEWER	Patrick Meybohm University Hospital Frankfurt, Department of Anesthesiology, Intensive Care Medicine and Pain Therapy
REVIEW RETURNED	17-Jul-2022

GENERAL COMMENTS	This is a very interesting study I have only a few major comments - The primary outcome is the mean difference in hemoglobin at 1 month. Hemoglobin levels at 1 month will likely be biased by RBC transfusions. How do the authors control for RBC transfusions and different RBC strategies, and thereby control for Hb level confounders? Differences in RBC transfusion will only be assessed after 3 months. In a worst case, control patients receive more RBC units and may have higher hemoglobin levels? - Sample size of 2x37 patients seems to be very low, how do the authors control for the bundle concept and different therapeutic interventions which may increase sample size? - Effect size: if the estimated control hb level would be 10.8 g/dl and the estimated effect size 1 g/dl, do the authors aim for a target hb level of 11.8 g/dl in the treatment group? This is reasonably very high after 1 months ICU therapy, and with questionable medical need. Why do the authors aim for a Hb of about 12 g/dl as the new target Hb level? There are no data supporting the hypothesis that 11.8 is better than 10.8 g/dl, and the impact on the different planned secondary outcomes is questionable. A delta of 1g/dl might be more important in a range of 8 vs 9g/dl, but both 10.8 and 11.8 g/dl are reasonably high without any clinical relevance. - Primary outcome and effect size: I would rather expect comparable hb levels between the groups in a range of 9-11g/dl but less RBC transfusions in the treatment group.

REVIEWER	Philipp Helmer University of Würzburg, Anaesthesiology
REVIEW RETURNED	11-Aug-2022

GENERAL COMMENTS	Dear Authors, I would like to congratulate you for this very exciting study protocol. Here, a very exciting question of the PBM is addressed in a methodologically challenging trial. Especially the customized drug therapy, as well as the consideration of blood draws in combination, raises expectations for exciting results of the study. However, the effect of allogeneic blood transfusions could have a systematic and relevant bias on the results. Here, a definition of tresholds for the indication of allogeneic blood transfusion would be fundamental. Why was the trial classified as a phase 2 trial (on clinicaltrials.gov)? In this case, classification as a phase 4 study might be more appropriate? Many thanks and the best for conducting the trial.

REVIEWER	Heyman Luckraz Mediclinic City Hospital, Cardiothoracic Surgery
REVIEW RETURNED	07-Sep-2022

GENERAL COMMENTS	The Authors Re: The Practical Anemia Bundle for Sustained Blood Recovery (PABST-BR) in Critical Illness: A Protocol for a Randomized Controlled Trial This is a well written and designed protocol as a pilot study to assess blood recovery in critically ill patients. The authors should consider the following: 1. Page 3 line 18 – do authors mean “Strengths and limitations”? 2. Patients’ anaemia has been grouped as either iron-responsive or inflammatory anaemias. How about B12 and Folate levels? Will these patients be included? If so, what treatment will they receive? 3. Patients will receive a fixed iron dose IV – why did the authors not consider a weight- dependent dose? 4. Will patients’ diet be monitored during and after hospital admission? 5. Primary outcome is the mean differences in Haemoglobin (Hb) level. How are the authors going to account for those patients who receive blood transfusion as their Hb level will be arbitrarily raised? 6. Are surgical patients included in the study? If so, how will the authors account for on-going acute blood loss post-randomisation?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Patrick Meybohm, University Hospital Frankfurt Comments to the Author:
This is a very interesting study

I have only a few major comments

- The primary outcome is the mean difference in hemoglobin at 1 month. Hemoglobin levels at 1 month will likely be biased by RBC transfusions. How do the authors control for RBC transfusions and different RBC strategies, and thereby control for Hb level confounders? Differences in RBC transfusion will only be assessed after 3 months. In a worst case, control patients receive more RBC units and may have higher hemoglobin levels?

  Response: These are excellent questions. First, we are collecting all RBC transfusion data during index hospitalization and through the first 3-months post-hospitalization. Second, we will assess differences in RBC transfusion utilization between groups during index hospitalization and through the first 3-months post-hospitalization. Given the study design, randomization balances the two study arms with respect to transfusions administered prior to

randomization. With regards to post-randomization transfusions, these are being evaluated as an outcome. In accordance with the United States Food and Drug Administration (FDA) ICH E9 guidelines for statistical principles for clinical trials, "It is not advisable to adjust the main analyses for covariates measured after randomization because they may be affected by the treatments." Hence, we will not be adjusting our primary analysis for post-randomization transfusions. However, a mediation analysis will be considered as a secondary analysis to determine whether the relationship between randomization group and hemoglobin concentrations is mediated by RBC transfusions. This has been added to the manuscript.

Page 9, "Differences in allogeneic RBC transfusion rates will be assessed through 3-months, and a mediation analysis may be performed to determine whether the relationship between randomization group and hemoglobin concentrations is mediated by RBC transfusions."

- Sample size of 2x37 patients seems to be very low, how do the authors control for the bundle concept and different therapeutic interventions which may increase sample size?

  Response: In this pilot trial, we are not evaluating each intervention separately. We are adequately powered for the primary outcome of changes in hemoglobin concentrations and will obtain necessary exploratory data for the subsequent multicenter trial in which different aspects of a treatment bundle may be evaluated separately.

- Effect size: if the estimated control hb level would be 10.8 g/dl and the estimated effect size 1 g/dl, do the authors aim for a target hb level of 11.8 g/dl in the treatment group? This is reasonably very high after 1 months ICU therapy, and with questionable medical need. Why do the authors aim for a Hb of about 12 g/dl as the new target Hb level? There are no data supporting the hypothesis that 11.8 is better than 10.8 g/dl, and the impact on the different planned secondary outcomes is questionable. A delta of 1g/dl might be more important in a range of 8 vs 9g/dl, but both 10.8 and 11.8 g/dl are reasonably high without any clinical relevance.

  Response: Patients will be enrolled with hemoglobin concentrations < 10 g/dL. The actual distribution of hemoglobin concentrations at enrollment may vary considerably, but generally will fall between 7 and 10 g/dL. Our previous data highlight that the mean hemoglobin of ICU survivors is 10.8 g/dL at 1-month post-discharge, albeit many do not reach this level. Additionally, our recent data (PMID 35103495) suggests that each 1 g/dL increase in 1-month post-hospitalization hemoglobin recovery is associated with fewer hospital readmissions and lower mortality through the first year after critical illness, suggesting that greater early hemoglobin recovery may indeed be associated with clinical benefit. In this pilot trial, we will be collecting such secondary outcome measures (i.e. readmissions, mortality, functional outcomes) to determine if there is signal for improved clinical outcomes with the anemia intervention.

- Primary outcome and effect size: I would rather expect comparable hb levels between the groups in a range of 9-11g/dl but less RBC transfusions in the treatment group.

  Response: Thank you for your perspective. We look forward to seeing the results.

Reviewer: 2

Dr. Philipp Helmer, University of Würzburg Comments to the Author:

- Dear Authors, I would like to congratulate you for this very exciting study protocol. Here, a very exciting question of the PBM is addressed in a methodologically challenging trial. Especially the customized drug therapy, as well as the consideration of blood draws in combination, raises expectations for exciting results of the study. However, the effect of allogeneic blood transfusions could have a systematic and relevant bias on the results. Here, a definition of thresholds for the indication of allogeneic blood transfusion would be fundamental.

  Response: Thank you for your comment, which was shared by reviewer 1 (see our earlier response). We will be evaluating differences in RBC transfusion utilization between groups.

With regards to RBC transfusion thresholds, institutional guidelines are in place and will be employed for both study arms (i.e. RBCs indicated for Hb < 7 g/dL or < 8 g/dL in those with myocardial ischemia or other signs of inadequate oxygen delivery). This has been added to the paper.

Page 8, "Transfusion practice for patients in both arms will occur in accordance with institutional transfusion guidelines (i.e., RBCs indicated for hemoglobin <7g/dL or <8 g/dL with concern for coronary ischemia or impaired end-organ oxygen delivery)."

- Why was the trial classified as a phase 2 trial (on clinicaltrials.gov)? In this case, classification as a phase 4 study might be more appropriate?

  Response: We believe that this trial is appropriately classified as phase 2. Safety will be monitored, although iron dextran and EPO are approved medications already available in practice and other protocol elements have limited safety concerns. We will assess feasibility of implementing this treatment protocol at the patient level, which provides some phase 1 elements, but most importantly we will evaluate for signals of efficacy of this novel treatment approach in a relatively limited number of subjects with the disease of interest. Assuming we show feasibility with signals of efficacy and safety in this phase 2 trial, we will then move forward with a multicenter phase 3 trial designed to clearly demonstrate efficacy and safety.

Many thanks and the best for conducting the trial.

Reviewer: 3
Dr. Heyman Luckraz, Mediclinic City Hospital Comments to the Author:
This is a well written and designed protocol as a pilot study to assess blood recovery in critically ill patients. The authors should consider the following:

1. Page 3 line 18 – do authors mean "Strengths and limitations"?

   Response: Yes. Thank you for noticing the error. The change has been made

2. Patients' anaemia has been grouped as either iron-responsive or inflammatory anaemias. How about B12 and Folate levels? Will these patients be included? If so, what treatment will they receive?

   Response: The reviewer is correct in that folate and B12 deficiencies can lead to anemia. However, it is generally acknowledged that anemia of inflammation and iron deficiency are overwhelmingly responsible for ICU-associated anemia, with non-iron nutritional deficiencies being rare in this setting. If a patient has known B12 and/or folate deficiency as the driver of anemia, these patients will not be approached for study enrollment.

3. Patients will receive a fixed iron dose IV – why did the authors not consider a weight-dependent dose?

   Response: A single fixed dose was chosen to minimize study complexity and potential for error. 1000 mg of iron dextran is considered a total dose infusion, such that it should provide complete resolution of iron deficits for most adults with iron deficiency. We have added additional discussion of this to the limitations section on page 16.

   Page 17, "Third, fixed doses administered at a single time point are being employed for both IV iron and EPO to minimize study complexity and the potential for error. Future studies may be needed to optimize dosing regimens in critical illness."

4. Will patients' diet be monitored during and after hospital admission?

   Response: We will not be monitoring diet during or after hospitalization in this trial.

5. Primary outcome is the mean differences in Haemoglobin (Hb) level. How are the authors going to account for those patients who receive blood transfusion as their Hb level will be

arbitrarily raised?

Response: Excellent question. Please see our response to reviewer #1, above.

6. Are surgical patients included in the study? If so, how will the authors account for on-going acute blood loss post-randomisation?

Response: Another astute observation. We will be including post-surgical patients. Patients with ongoing hemorrhage or recent large-volume hemorrhage (i.e. ≥10 units within the 48 hours preceding enrollment) will not be included. We have added this exclusion criterion to Table 1. However, it is likely that some patients (both surgical and medical) may experience acute blood loss post-randomization irrespective of which arm they are randomized to.

VERSION 2 – REVIEW

REVIEWER	Patrick Meybohm University Hospital Frankfurt, Department of Anesthesiology, Intensive Care Medicine and Pain Therapy
REVIEW RETURNED	25-Oct-2022

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Philipp Helmer University of Würzburg, Anaesthesiology
REVIEW RETURNED	21-Oct-2022

GENERAL COMMENTS	Dear Authors, thank you for your response. I have no further comments. with best regards

REVIEWER	Heyman Luckraz Mediclinic City Hospital, Cardiothoracic Surgery
REVIEW RETURNED	26-Oct-2022

GENERAL COMMENTS	This is a well set up study. The queries have been addressed. Looking forward to the results