PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Restrictive transfusion strategy for critically injured patients (RESTRIC) trial: A study protocol for a cluster-randomised, crossover non-inferiority trial
AUTHORS	Hayakawa, Mineji; Tagami, Takashi; Iljima, Hiroaki; Kudo, Daisuke; Sekine, Kazuhiko; Ogura, Takayuki; Yumoto, Tetsuya; Kondo, Yutaka; Endo, Akira; Ito, Kaori; Matsumura, Yosuke; Kushimoto, Shigeki

VERSION 1 – REVIEW

REVIEWER	Professor Mike Murphy 1. University of Oxfor 2. NHS Blood & Transplant 3. Oxford University Hospitals United Kingdom
REVIEW RETURNED	25-Mar-2020

GENERAL COMMENTS	This is an ambitious trial of an important research question, namely the optimal target for haemoglobin concentration (Hb) for the transfusion of critically injured patients. The design of the study as a cluster-randomised trial is an interesting one. The protocol should include an explanation about the choice of this design rather than individual patient randomisation. Conducting a cluster-randomised trial can be challenging especially in acute care conditions.Was any feasibility study conducted to determine:- - the proportion of patients consenting to enter the trial? - the compliance with the Hb targets for red blood cell transfusion, especially in acutely bleeding patients? - the willingness of centres to switch to a different transfusion strategy after 1 year? Obtaining informed patient consent to enter the trial may be challenging. There appears to be no allowance in the trial protocol for patients initially unable themselves or without a representative to provide consent. The protocol should provide information to address this. Other points 1. Did the authors consider having Hb at 28 days as a secondary outcome measure? 2. There is a mixture of English and American spelling e.g. 'ischemia' on page 13. 3. It seems surprising that one of the authors of the protocol is employed by a pharmaceutical company.

REVIEWER	Paolo Rebulla Department of Transfusion Medicine and Hematology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, via Francesco Sforza 35, 20122 Milan, Italy
REVIEW RETURNED	04-May-2020

GENERAL COMMENTS	This is an interesting study aimed at evaluating the clinical outcome of transfusion strategies with lower versus higher Hb levels in the acute phase (1-7 days) of trauma patients. The protocol is described in detail and the authors report the fundamental methodological elements of cluster randomized trials. Some items of clarification could improve the quality of the manuscript, as follows: 1) Severe adverse events: please report the reference system used for SAE 2) Non-inferiority margin: please describe the rationale for selecting a 3% margin and the clinical relevance of this margin 3) Non-inferiority margin: please clarify if 3% is the upper limit of the 95% CI 4) From table 2 it appears that Hb levels will not be reported after 7 days. Based on the expectation that this data will be largely available, it could contribute to the analysis of causes of mortality at 28 days 5) Spirit checklist: item 30 requires specification of measures for indemnity of patients suffering damage during the study, but this was not reported 6) Informed consent form. This is usually reported in trial protocols.

VERSION 1 – AUTHOR RESPONSE

To Professor Mike Murphy,

Thank you very much for reviewing our manuscript and offering valuable advice.

We have provided point-by-point responses to your comments and have revised the manuscript accordingly. The revised text has been highlighted in yellow for ease of review.

Conducting a cluster-randomised trial can be challenging especially in acute care conditions. Was any feasibility study conducted to determine:-

- the proportion of patients consenting to enter the trial?

- the compliance with the Hb targets for red blood cell transfusion, especially in acutely bleeding patients?

- the willingness of centres to switch to a different transfusion strategy after 1 year?

Response: Thank you for your comments. I am sorry that we have not performed the feasibility study for this trial. However, until December 2019, 351 patients were eligible for our trial, and 161 (46%) patients consented to be included in the trial.

As same as real clinical settings, we defined the “target” level of Hb, but not current level of Hb, for the intervention of trial in each group. (This point was described in the Intervention section.) However, because the changes of actual measured Hb level is important; we will collect Hb levels measured in various timings.

Before participating in the trial, we explained to each centre to switch to a different transfusion strategy after 1 year, and each centre consented to the switching.

Obtaining informed patient consent to enter the trial may be challenging. There appears to be no allowance in the trial protocol for patients initially unable themselves or without a representative to provide consent. The protocol should provide information to address this.

Response: Thank you for your valuable comment. As you have indicated, obtaining informed patient consent to enter the trial was very challenging for severe trauma patients. Therefore, we applied the cluster-randomised design for the trial. The allocated transfusion strategy is posted in each hospital in order to provide opt-out opportunities to patients and their next of kin. During an initial phase after arrival at the emergency department, the allocated transfusion strategy will be applied for all trauma patients in each participating hospital. After obtaining consent from patients or their representatives, the patients will be registered to the trial, and the transfusion strategy will be applied until the defined period. If the registration to the trial is declined, the transfusion strategy will be completed based on the physician’s decision. This information is described additionally in the trial design section.

Other points

1. Did the authors consider having Hb at 28 days as a secondary outcome measure?

Response: In our trial, Hb at 28 days is not measured because almost all the trauma patients will have been discharged already at 28 days after the admission.

2. There is a mixture of English and American spelling e.g. 'ischemia' on page 13.

Response: Thank you for your observation. We have repeatedly performed careful English language editing.

3. It seems surprising that one of the authors of the protocol is employed by a pharmaceutical company.

Response: The planning of our trial started in 2017. At the planning of the trial, Hiroaki Iijima belonged to the Clinical Research and Medical Innovation Center, Hokkaido University Hospital. After the fix to the statistical plan, he moved to Amgen Astellas BioPharma K.K. (September 2019). This information has been added to the author's information section.

To Professor Paolo Rebulla,

Thank you very much for reviewing our manuscript and offering valuable advice.

We have provided point-by-point responses to your comments and have revised the manuscript accordingly. The revised text has been highlighted in yellow for ease of review.

1) Severe adverse events: please report the reference system used for SAE

Response: Significant adverse events (SAEs) will be recorded immediately in the patient's medical record in each hospital and in the electronic data capture system (NorthNet, https://www.crmic-huhp.jp/northnet/edc/), which are same as the system that recorded the assessment data of patients. According to your comment, this information has been described in the Safety monitoring section.

2) Non-inferiority margin: please describe the rationale for selecting a 3% margin and the clinical relevance of this margin

Response: Thank you for your valuable comment. We have referenced previous large clinical trials in the same field and defined the non-inferiority margin. This information has been added in the sample size section in the revised manuscript.

3) Non-inferiority margin: please clarify if 3% is the upper limit of the 95% CI

Response: Thank you for your comment. This is non-inferiority trial; thus, we have set the lower limit of the 95% CI to not exceed the non-inferiority margin at the sample size calculation. Therefore, we have added the following sentence in the statistical plan section; "Therefore, we will evaluate whether the lower limit of the 95% confidence interval of P_0-P_1 exceeds the non-inferiority margin (3%) or not."

4) From table 2 it appears that Hb levels will not be reported after 7 days. Based on the expectation that this data will be largely available, it could contribute to the analysis of causes of mortality at 28 days

Response: Thank you for your comment. As you pointed out, we do not collect Hb levels after 7 days, because of the following three reasons; 1) The main purpose of trial is to clarify the effects of restrictive transfusion strategy, but not low Hb levels in severe trauma patients. 2) The transfusion

strategy is applied until maximum 7 days after admission. 3) Almost all the trauma patients will have already been discharged from the hospital at 28 days after admission.

I am sorry to have not been able to change the protocol of collection of Hb levels, because our trial has started.

5) Spirit checklist: item 30 requires specification of measures for indemnity of patients suffering damage during the study, but this was not reported

Response: I am sorry for my misunderstanding about the Spirit checklist. In our trial, there are not post-trial care and compensation to patients who suffer harm. Therefore, we have revised the SPIRIT checklist.

6) Informed consent form. This is usually reported in trial protocols.

Response: Thank you for your suggestion. We have provided the Trial Information form and patient consent form in Japanese as supplementary files. Furthermore, we do not use the patient consent form in English in our settings, but we have provided the patient consent form translated to English as supplementary files.

VERSION 2 – REVIEW

REVIEWER	Prof Mike Murphy NHS Blood & Transplant; Oxford University Hospitals; University of Oxford, UK
REVIEW RETURNED	09-Jun-2020

GENERAL COMMENTS	In my opinion, the authors have responded satisfactorily to the reviewers' comments.

REVIEWER	Paolo Rebulla Department of Transfusion Medicine and Hematology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
REVIEW RETURNED	09-Jun-2020

GENERAL COMMENTS	I believe that the authors have responded satisfactorily to all referees' comments