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Restrictive transfusion strategy for critically injured patients (RESTRIC) trial: a study protocol for a cluster-randomised, crossover non-inferiority trial

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ABSTRACT

Introduction Resuscitation using blood products is critical during the acute postinjury period. However, the optimal target haemoglobin (Hb) levels have not been adequately investigated. With the restrictive transfusion strategy for critically injured patients (RESTRIC) trial, we aim to compare the restrictive and liberal red blood cell (RBC) transfusion strategies.

Methods and analysis This is a cluster-randomised, crossover, non-inferiority trial of patients with severe trauma at 22 hospitals that have been randomised in a 1:1 ratio based on the use of a restrictive or liberal transfusion strategy with target Hb levels of 70–90 or 100–120 g/L, respectively, during the first year. Subsequently, after 1-month washout period, another transfusion strategy will be applied for an additional year. RBC transfusion requirements are usually unclear on arrival at the emergency department. Therefore, patients with severe bleeding, which could lead to haemorrhagic shock, will be included in the trial based on the attending physician's judgement. Each RBC transfusion strategy will be applied until 7 days postadmission to the hospital or discharge from the intensive care unit. The outcomes measured will include the 28-day survival rate after arrival at the emergency department (primary), the cumulative amount of blood transfused, event-free days and frequency of transfusion-associated lung injury and organ failure (secondary). Demonstration of the non-inferiority of restrictive transfusion will emphasise its clinical advantages.

Ethics and dissemination The trial will be performed according to the Japanese and International Ethical guidelines. It has been approved by the Ethics Committee of each participating hospital and The Japanese Association for the Surgery of Trauma (JAST). Written informed consent will be obtained from all patients or their representatives. The results of the trial will be disseminated to the participating hospitals and board-certified educational institutions of JAST, submitted to peer-reviewed journals for publication, and presented at congresses.

Strengths and limitations of this study

- During the acute postinjury period, the appropriate strategy for red blood cell transfusion has not been investigated.
- This trial will be the first to determine the optimal haemoglobin level during the acute postinjury period in patients with severe trauma.
- This multicentre trial will have a cluster-randomised, crossover non-inferiority design.
- The two study interventions will be restricted or liberal red blood cell transfusion initiated immediately after the patient's arrival at the emergency department.
- Each red blood cell transfusion strategy will be defined by a target haemoglobin level rather than by the actual patient's haemoglobin level.

Trial registration number UMIN Clinical Trials Registry; UMIN000034405. Registered 8 October 2018.

INTRODUCTION

Bleeding is a major cause of death after severe trauma. Although early haemostatic procedures are most important, resuscitation using crystalloid and blood products also plays a crucial role in the early phase of management of patients with severe trauma. While the transfusion of fresh frozen plasma has been widely evaluated in the management of trauma-associated coagulopathy during the acute postinjury period,[1–7] the transfusion of red blood cells (RBCs) has not been investigated adequately, and the optimal target levels of haemoglobin (Hb) in the early phase of treatment remain unclear.

The European guidelines for the management of major bleeding and coagulopathy recommend target Hb levels of 70–90 g/L.[8]

This is based mainly on the results of a posthoc analysis of the Transfusion Requirements in Critical Care (TRICC) trial,[9] which compared a restrictive transfusion strategy (target Hb level: 70–90 g/L) with a liberal transfusion strategy (target Hb level: 100–120 g/L).[10] However, as the TRICC trial included critically ill patients after admission to intensive care units (ICUs), information regarding the patient characteristics, haemostatic procedures and transfusion before admission to the ICUs remains unclear.[10] Furthermore, the trial excluded patients with active blood loss.[10] Therefore, it is not appropriate to apply the results of this trial and its posthoc analysis to patients in the early phase of severe trauma.[9 10] The European guidelines also state that 'it should be emphasised that this study was neither designed nor powered to answer these questions with precision' in the rationale section.[8]

A low Hb level is a possible cause of hypoxic damage to various organs. In patients with traumatic brain injury, a low Hb level is associated with particularly concerning neurological outcomes.[11] Recently, a randomised controlled trial that compared two Hb transfusion thresholds (70 g/L or 100 g/L) in patients with traumatic brain injury indicated no differences in the neurological outcomes and mortality rates between the use of low and high Hb transfusion thresholds.[12] However, 38% of the patients included in that study were not transfused with any packed RBCs.[12]

To address the above-mentioned lack of clarity regarding the clinical impacts of a restrictive RBC transfusion strategy in trauma patients during the acute post-injury period, we are conducting a cluster-randomised, crossover non-inferiority trial to compare restrictive and liberal RBC transfusion strategies.

METHODS AND ANALYSIS

Trial design

The restrictive transfusion strategy for critically injured patients (RESTRIC) trial is a cluster-randomised, crossover non-inferiority multicentre trial of patients with severe trauma. This pragmatic trial aims to reproduce real-world settings as closely as possible. The RESTRIC trial applies a cluster-randomised design that enables the initiation of study interventions immediately after arrival at the emergency department (ED) and a crossover design to reduce the confounding effects between different hospitals.

Twenty-two hospitals in Japan are participating in the RESTRIC trial (table 1). These hospitals are tertiary emergency medical facilities that provide emergency and intensive care treatments to patients with severe trauma. The participating hospitals have been randomised into two study schedules at a 1:1 ratio based on a precreated random assignment table to either a restrictive transfusion strategy (target Hb level: 70–90 g/L) or a liberal transfusion strategy (target Hb level: 100–120 g/L). After the randomisation, the hospitals will apply the first transfusion strategy for 1 year (first study period). After a washout period of 1 month, after the end of the first study period, the second transfusion strategy will be applied for another 1 year (second study period; figure 1).

The allocated transfusion strategy is posted in each hospital in order to provide opt-out opportunities to patients and their next of kin. The allocated transfusion strategy will be applied for all trauma patients during the initial phase after arrival at the ED. After obtaining the consent for registration from the patients or their representatives, the patients will be registered in the trial and the transfusion strategy will be applied until a defined period. If the registration to the trial is declined, the transfusion strategy will be continued based on the physician's decision.

Patients

On arrival at the ED, the requirement for RBC transfusion is usually unclear. Therefore, the inclusion criteria include trauma patients aged ≥20 years with one of the following complications based on the judgement of the attending physician (figure 2):

1. Severe bleeding that can result in circulatory shock.
2. Suspicion of such bleeding after arrival at the ED.
3. Possibility of inducing such bleeding by surgical procedures during the acute phase of trauma.

The following exclusion criteria have been set:

1. Cardiac arrest before or on arrival at the hospital.
2. Transfer from another hospital.
3. Physician's decision to withdraw active treatment at the initial assessment.
4. Severe burn injuries (≥15% of the body surface).
5. Pregnancy.
6. Chronic anaemia (Hb level ≤70 g/L).
7. Known objection to blood transfusions.

Intervention

In severe trauma patients with active bleeding, RBC transfusion is frequently initiated before confirming a decrease in Hb levels. Therefore, each RBC transfusion strategy is defined by the target Hb level rather than the current Hb level. The timing of RBC transfusion initiation in a patient with active bleeding is determined by the attending physician based not only on the Hb levels but also on haemodynamic instability. Either of the RBC transfusion strategies will be applied to patients until (1) 7 days after admission to the hospital, (2) discharge from the ICU, (3) decision to withdraw active treatment or (4) death.

Assessments and follow-up

Clinical assessments and treatments will be performed as necessary based on the attending physician's judgement. The schedule of trial assessments is presented in table 2. The assessment data will be recorded in the electronic trial data capture system (NorthNet, https://www.crmic-huhp.jp/northnet/edc/). Patients will be followed for 28 days. If a patient is discharged from the hospital prior to 28 days after arrival at the ED, the investigators will

Table 1 List of participating hospitals and ethics committee

Participating hospitals	Ethics committees
Principal institution	
Department of Emergency and Critical Care Medicine, Tohoku University Hospital	Ethics Committee Tohoku University Graduate School of Medicine
Project management	
Department of Emergency Medicine, Hokkaido University Hospital	The Institutional Review Board of Hokkaido University Hospital
Other participating institutions	
Advanced Critical Care and Emergency Centre, Okayama University Hospital	Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, Ethics Committee
Advanced Critical Care Centre, Gifu University Hospital	Medical Review Board of Gifu University Graduate School of Medicine
Advanced Emergency and Critical Care Centre, Saitama Red Cross Hospital	Hospital ethical committee of Saitama Red Cross
Advanced Trauma, Emergency and Critical Care Centre, Oita University Hospital	The Institutional Review Board of Interventional Clinical Research of Oita University Hospital
Department of Emergency Medicine, Gunma University Graduate School of Medicine	Institutional Review Board of Gunma University Hospital
Department of Acute Care Surgery, Shimane University Faculty of Medicine	The Shimane University Institutional Committee on Ethics
Department of Emergency and Critical Care Medicine, Chiba University Graduate School of Medicine	Chiba University Certified Clinical Research Review Board
Department of Emergency and Critical Care Medicine, Fukuoka University Hospital	Institutional Review Board of Fukuoka University Hospital
Department of Emergency and Critical Care Medicine, Japan Red Cross Maebashi Hospital	Research Review Board of Japan Red Cross Maebashi Hospital
Department of Emergency and Critical Care Medicine, Juntendo University Urayasu Hospital	The Ethics Committee of the Juntendo University Urayasu Hospital
Department of Emergency and Critical Care Medicine, Nippon Medical School	Ethics Committee of Nippon Medical School Hospital
Department of Emergency and Critical Care Medicine, Nippon Medical School Tama Nagayama Hospital	Ethics Committee of Nippon Medical School Tamanagayama Hospital
Department of Emergency and Critical Care Medicine, Tokyo Saiseikai Central Hospital	Research Ethics Committee, Tokyo Saiseikai Central Hospital
Department of Emergency and Critical Care Medicine, Wakayama Medical University	The Ethical Review Board of Wakayama Medical University
Department of Emergency Medicine, Division of Acute Care Surgery, Teikyo University School of Medicine	Teikyo University Institutional Review Board
Emergency and Critical Care Centre, Kochi Health Sciences Centre	Institutional Review Board, Kochi Health Sciences Center
Senri Critical Care Medical Centre, Saiseikai Senri Hospital	Ethical committee Saiseikai Senri Hospital
Senshu Trauma and Critical Care Centre, Rinku General Medical Centre	Ethics Committee for Clinical Research, Rinku General Medical Centre
Shock and Trauma Centre, Nippon Medical School Chiba Hokusoh Hospital	The Ethical Review Board of Nippon Medical School Chiba Hokusoh Hospital
Trauma and Acute Critical Care Centre, Tokyo Medical and Dental University Hospital of Medicine	Medical Research Institute Tokyo Medical and Dental University

contact the patient (or their representative, as appropriate) by telephone to collect information regarding the patient's status.

Safety monitoring

A safety monitoring board comprising two independent experts who are not involved in the conduct of the trial will

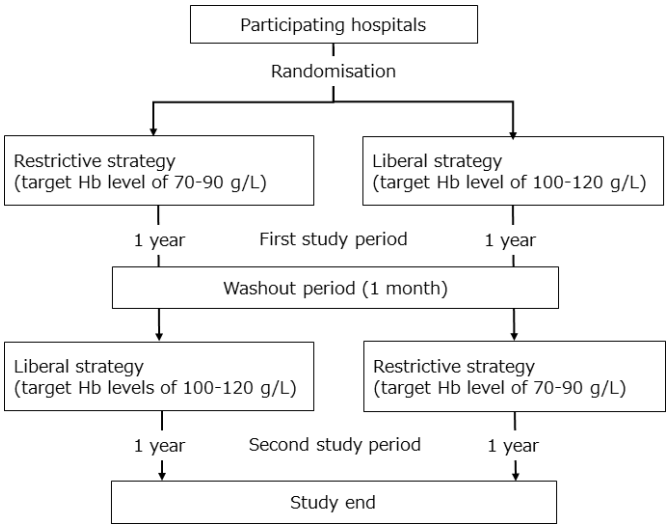

Figure 1 Flowchart of the randomisation and crossover of the participating hospitals. Hb, haemoglobin.

oversee the safety of the trial. Significant adverse events (SAEs) will be recorded immediately in the patient's medical record 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. The treating physician will immediately report any SAEs to the site investigator, who will in turn report them to the chief of each site and the principal investigator. The principal investigator will then consult with the safety monitoring board about the SAEs. The board will review and examine the report and send written recommendations made in response to the principal investigator.

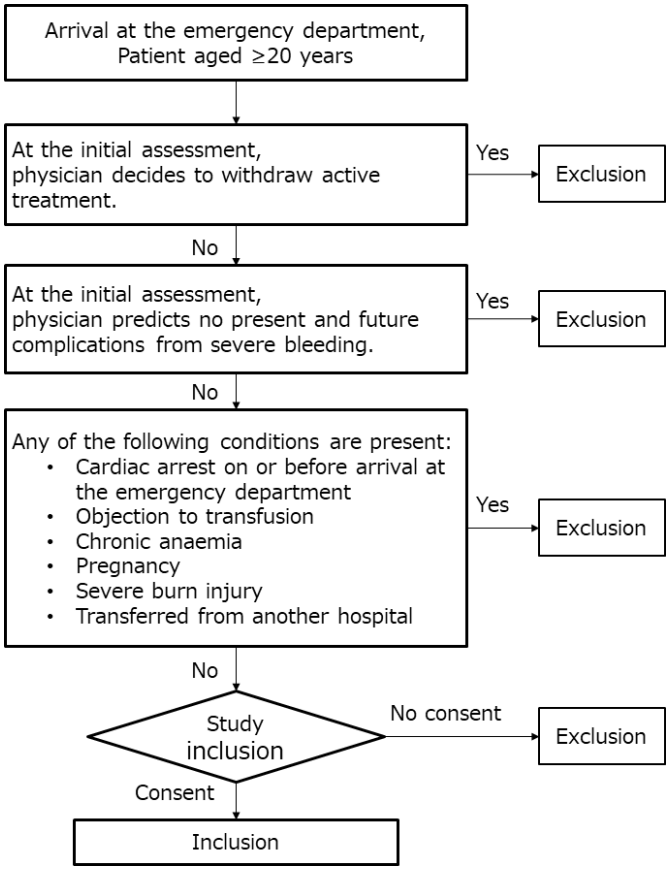

Figure 2 Flowchart of the patient enrolment process.

Primary outcome

To evaluate the non-inferiority of the restrictive transfusion strategy to the liberal transfusion strategy, we will assess the 28-day survival rate after arrival at the ED (tables 2 and 3) as the primary outcome measure. Patients with incomplete information regarding survival/death on the 28th day after arrival at the ED will be defined as dropout and will be excluded from the primary outcome analysis.

Secondary outcomes

The secondary outcome measures will be: (1) the time to death during the first 28 days, (2) in-hospital survival rate, (3) cumulative amounts of RBC concentrate, fresh-frozen plasma and platelet cell concentrate transfused during days 1, 7 and 28, (4) ventilator-free, catecholamine-free and ICU-free days during the first 28 days, (5) frequency of organ failure (renal, hepatic and respiratory) during the first 7 days, (6) rates of each complication (deep venous thrombosis, pulmonary embolism, cerebral infarction, myocardial infarction, bowel ischaemia, transfusion-associated lung injury (TRALI) and sepsis) during the first 28 days and (7) the Glasgow Outcome Scale at discharge from the hospital (tables 2 and 3).[13] If the patient dies during the first 28 days after admission to the hospital, each event-free day will be defined as zero. Renal failure is defined as stage III as per the Kidney Disease Improving Global Guidelines.[14] Hepatic failure is defined as a total bilirubin level ≥6 mg/dL, as per the Sequential Organ Failure Assessment score.[15] Respiratory failure is defined as moderate acute respiratory distress syndrome as per the Berlin definition.[16] Deep venous thrombosis, pulmonary embolism and cerebral infarction will be diagnosed via clinical imaging, whereas myocardial infarction and bowel ischaemia will not be diagnosed solely from the elevation of cardiac biomarkers and laboratory data, respectively. TRALI is defined according to the Toronto definition,[17] and sepsis is defined according to sepsis-3.[18]

Sample size

In our previous retrospective multicentre observational study, wherein data were collected from 796 patients with severe trauma from 15 hospitals during a 1-year period,[19–26] 241 patients received RBC concentrates during the first 24 hours after arrival at the ED and 25% of the patients transfused with RBC concentrates died within 28 days after arrival at the ED. Based on these results, we assumed a mortality rate of 25% at 28 days after arrival in the ED among patients receiving a liberal RBC transfusion strategy. To evaluate the non-inferiority of the restrictive versus liberal transfusion strategy at 28 days postarrival at the ED, we set both the interclass and interperiod correlation coefficients at 0.05 and the non-inferiority margin

Table 2 Schedule of assessments

	Arrival at ED	6 hour	12 hours	24 hours	48 hours	Day 7	Discharge from ICU	Discharge from hospital	Day 28
Informed consent	○								
Check inclusion/exclusion criteria	○								
Patient assessment	○								
Physiologic severity	○								
Abbreviated Injury Scale	○								
Surgical intervention and IVR	├──○──┤								
Laboratory data	○								
Haemoglobin level	├	─	─○─	─	┤				
Cumulative amount of transfusion		○	○	○	○	○			○
Organ failure (renal/respiratory/hepatic)	├	─	─○─	─	┤				
TRALI	├	─	─	─	─○─	─	─	─	┤
Complications	├	─	─	─	─○─	─	─	─	┤
Mortality							○	○	○
Discharge destination								○	
Glasgow outcome scale								○	
Event-free days (free of ventilator/catecholamine/ICU)									○

Complications include deep venous thrombosis, pulmonary embolism, acute myocardial infarction, ischaemic bowel necrosis and sepsis.
IVR, interventional radiology; TRALI, transfusion-related acute lung injury; ICU, intensive care unit.

Table 3 Primary and secondary outcomes

Outcome	Definition/annotation
Primary outcome	
28 day survival rate after arrival at the ED	Patients whose survival/death information on 28th day after arrival at the ED is unclear are defined as drop-outs and will be excluded from the primary outcome analysis
Secondary outcome	
Time to death during the first 28 days after arrival at the ED	
In-hospital survival rate	
Cumulative transfusion amounts	
Red blood cell concentrate	Cumulative amounts during the first 1, 7 and 28 days after arrival at the ED
Fresh-frozen plasma	Cumulative amounts during the first 1, 7 and 28 days after arrival at the ED
Platelet concentrate	Cumulative amounts during the first 1, 7 and 28 days after arrival at the ED
Event-free days during the first 28 days after arrival at the ED	
Ventilator-free days	When the patient dies during the first 28 days after the arrival at ED, the free days are defined as zero
Catecholamine-free days	When the patient dies during the first 28 days after the arrival at ED, the free days are defined as zero
ICU-free days	When the patient dies during the first 28 days after the arrival at ED, the free days are defined as zero
Organ failure during the first 7 days after arrival at the ED	
Renal failure	Stage III defined by the Kidney Disease Improving Global Guidelines
Hepatic failure	Total bilirubin level ≥6 mg/dL as per the Sequential Organ Failure Assessment score
Respiratory failure	Moderate acute respiratory distress syndrome according to the Berlin definition
Complications during in-hospital stay or the first 28 days after arrival at the ED	
Deep venous thrombosis	Presence or absence should be diagnosed using clinical imaging
Pulmonary embolism	Presence or absence should be diagnosed using clinical imaging
Cerebral infarction	Presence or absence should be diagnosed using clinical imaging
Acute myocardial infarction	Presence or absence should not be diagnosed using only an elevation of cardiac biomarkers
Bowel ischaemia	Presence or absence should not be diagnosed using laboratory data
Transfusion-associated lung injury	Presence, possibility or absence are defined using the Toronto definition
Sepsis	Presence or absence should be diagnosed using the Sepsis-3 definition
Glasgow outcome scale score at discharge from the hospital	Good recovery, moderate disability, severe disability, persistent vegetative state or death

ED, emergency department; ICU, intensive care unit.

at 3%. The non-inferiority margin was defined based on statistically acceptable tolerance and clinically acceptable margin referenced previous large clinical trials in the same field[10 27–30]

Assuming that 17 hospitals participate and are randomised as a cluster, the present study would require the inclusion of 170 patients for each of the transfusion strategies to reach a power of 80% and a one-sided alpha level of 2.5%, based on a previous study.[31] Therefore, we set the total target sample size for this study at 400 patients, considering a possible variation in the cluster size, the inclusion of non-appropriate patients and drop-outs during follow-up. According to previous studies, this number of patients will allow us to study the outcomes for 2 years.[19–26]

Statistical plan

All analyses of the primary outcome will be adjusted for clustering within sites. The analysis will use a mixed model with adjustment for intervention, the period as a fixed effect and the sites and the interaction of site with period as a random effect.[32] The non-inferiority margin will be set at P_0–P_1 <0.03 (P_0, 28-day survival rate for liberal transfusion; P_1, 28-day survival rate for restrictive transfusion). Therefore, we will evaluate whether the lower limit of the 95% CI of P_0–P_1 exceeds

the non-inferiority margin (3%) or not. We will use the full analysis set for our primary outcome analysis after excluding cases with missing primary outcome values. We will follow the principle of intention-to-treat for the primary analysis and a per-protocol for sensitivity analysis to ensure that no cases deviate intentionally from the target Hb levels.

The secondary outcomes will be analysed as follows. (1) Kaplan-Meier curves with log rank statistics will be used to assess the survival rate during the first 28 days after arrival at the ED, (2) the number of in-hospital survival patients will be tabulated, (3) summary statistics of the cumulative amounts of transfused RBC concentrate, fresh-frozen plasma and platelet cell concentrate during days 1, 7 and 28 after arrival at the ED will be created using graphs plotted over time, (4) summary statistics of the event-free days (ie, ventilator-free, catecholamine-free and ICU-free days) will be calculated, (5) the proportions of organ failure and complications will be calculated, (6) the Glasgow Outcome Scale will be measured at discharge from hospital.

Subgroup analyses will be performed to investigate the effects of the interventions on patients according to sex, age (<60 or ≥60 years), Injury Severity Score (<16 or ≥16 years), head trauma and performance of definitive surgical procedures within 6 hours of arrival at the ED. The results of both unadjusted and covariate data-adjusted analyses will be assessed. Furthermore, we will perform a posthoc power analysis if the numbers of the participating institutions and included patients differ from the planned numbers.

Patient and public involvement

No patient is involved.

ETHICS AND DISSEMINATION

Ethical approval and consent to participate

The clinical trial will be conducted according to the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Health, Labour and Welfare of Japan and the Japanese Ministry of Education, Culture, Sports, Science and Technology. Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our trial. The present trial is registered with the UMIN Clinical Trials Registry and has been approved by the Ethics Committee of each participating hospital (table 1) and the Japanese Association for the Surgery of Trauma (Ethics Committee of the Japanese Association for the Surgery of Trauma). Written informed consent will be obtained from all patients or their representatives. The trial information form in Japanese and patient consent forms in Japanese and English were provided as supplement files (online supplemental files 1-3).

Dissemination

The results of trial will be disseminated to the participating hospitals and board-certified educational institutions of The Japanese Association for The Surgery of Trauma, submitted to peer-reviewed journals for publication, and presented at congresses.

Expected outcomes

The RESTRIC trial will compare the outcomes of the restrictive versus liberal RBC transfusion strategy in trauma patients during the acute postinjury period. To the best of our knowledge, the RESTRIC trial will be the first to clarify the optimal target Hb levels in patients with severe trauma during this period.

Although previous studies, such as the TRICC trial and its posthoc analysis,[9 10] initiated the study interventions after admission to the ICU, the RESTRIC trial has been designed to initiate the study interventions immediately after arrival at ED and to continue these interventions through the early phase of severe trauma. In patients with severe trauma, management before admission to an ICU is as important as that after admission to an ICU. If the restrictive RBC transfusion strategy is found to be non-inferior to the liberal RBC transfusion strategy, the former will be considered advantageous in clinical settings during the acute postinjury period because it will help reduce the total amount of RBC transfusion. This reduction in RBC transfusion will reduce (a) the risk of transfusion-related complications such as TRALI, (b) RBC transfusion-related immunomodulation and (c) the costs associated with RBC transfusion.[17 33]

Trial status

At first, the trial protocol V.1.3 was approved at 11 October 2018. The latest protocol is V.1.7 that has been approved at 19 December 2019 after minor changes (online supplemental file 4). In May 2019, 12 participating institutions were randomised as a cluster, and the trial was started. The first patient was included on 11 May 2019. Subsequently, 10 more institutions have joined the trial and have been randomised. The last participating institution began the trial in October 2019. Patients will be recruited until October 2021 and followed up thereafter.

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Contributors MH conceived and designed the RESTRIC trial and drafted the manuscript. TT drafted the statistical plan. HI calculated the sample size and developed the statistical plan. SK is the principal investigator and supervised the planning of the RESTRIC trial. MH, TT, HI, DK, KS, TO, TY, YK, AE, KI, YM and SK discussed the plan of the RESTRIC trial, revised the manuscript for important intellectual content and read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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