West China Liu's Score for Individualized Red Cells Transfusion Strategy in Non-Cardiac Surgery: Study Protocol for A Multicenter, Randomized, Controlled Trial
Ren Liao, Hao-Rui Sun, and Jin Liu

ABSTRACT

Background: Transfusion trigger and target for surgical patients with hemoglobin level between 6-10 grams per deciliter (gram per deciliter) is not implemented worldwide. The decision of whether red cells should be given to these patients is often made according to the experience of clinicians without specific clinical or laboratory evidence. Based on the physiology of the balance between oxygen supply and consumption, we developed the West China Liu's Score that will help clinicians to make individualized transfusion decisions for patients undergoing elective non-cardiac major surgery. The aim of this study is to determine whether the individualized red cells transfusion strategy, when compared with restrictive transfusion strategy (red cells transfusion trigger based on the judgment of physicians according to current transfusion guidelines) and liberal transfusion strategy (red cells transfusion trigger of 10 grams per deciliter), will decrease red cells transfusion requirement without increasing mortality or postoperative complications, or delaying incision healing, or increasing the cost of hospitalization.

Methods and Design: This trial is a prospective, multicenter, randomized controlled trial that will test the superiority of the individualized transfusion strategy to restrictive transfusion strategy and liberal transfusion strategy in terms of reducing red cells transfusion demands safely and effectively. A total of 4200 patients undergoing elective major surgery with estimated intra-operative blood loss more than 1000 ml or 20% of total blood volume and perioperative hemoglobin less than 10 grams per deciliter will be randomized into individualized-strategy group, restrictive-strategy group, and liberal-strategy group. The primary outcomes of the study are the incidences of red cells transfusion and combination of in-hospital death for any reason and serious complications.

Discussion: The individualized transfusion strategy guided by application of West China Liu's score will provide a new insight on the perioperative transfusion practice and new clinical proof for the transfusion guidelines.

Trial Registration: This trial was registered at ClinicalTrials.gov (identifier NCT01597232) on 14 May 2012.
Allogeneic blood transfusion is an essential integral part for surgeries to be conducted safely in modern medicine. For decades, the decision for red cell transfusion was based on "10/30 rules", a liberal transfusion strategy, i.e. transfuse to keep hemoglobin level not less than 10 grams per deciliter or hematocrit not less than 30% (1). However, in recent years, in addition to inadequate blood supply in some countries, a number of potential transfusion-related complications, such as infection (bacterial, viral or prion), acute lung injury, and immunomodulation with resultant reactivation of cancer and tuberculosis have brought the liberal transfusion strategy into spotlight (2). Hence, it is common practice in modern medicine to minimize the perioperative allogeneic blood transfusion worldwide. In various international guidelines on perioperative blood transfusion, red cells transfusion is always not recommended in patients with hemoglobin level above 10 grams per deciliter, and is required when hemoglobin level decreases to 6 or 7 gram per deciliter (3-5). This is a restrictive transfusion strategy. Meanwhile, the decision for red cells transfusion when hemoglobin level is between 6-10 grams per deciliter, which is common in perioperative surgical patients, depends on patients’ cardiopulmonary reserve and oxygen consumption. As there are currently no objective methods to evaluate the status of global oxygen demanding and consumption (O₂ D/C), red cells transfusion decision is often made based on the subjective judgment of attending physicians.

The goal of red cells transfusion is restoration of the O₂ D/C balance (6), which is directly proportional to the cardiac output, hemoglobin level, and blood oxygen saturation, but inversely proportional to body oxygen consumption mainly determined by basal metabolic rate or body temperature (7). Therefore, red cells transfusion is likely required in a patient with decreased oxygen carrying capacity who requires inotrope infusion in order to maintain the cardiac output and (or) increase in inspired oxygen concentration to keep the pulse oximetry oxygen saturation (SpO₂) ≥95%. On the other hand, red cells transfusion may be needed to meet the increased oxygen demand, such as fever. Furthermore, a higher oxygen carrying capacity is desirable in patients with coronary artery stenosis. All things considered, we proposed a West China Liu's Score to guide the red cells transfusion for surgical patients (Table 1).

Liu's score is proposed to evaluate the red cells transfusion trigger based on each individualized patient status and the patient's immediate hemoglobin level, and further to determine the target hemoglobin level. So Liu's score is the red cell transfusion trigger and target (T&T) score. It is a dynamic score whenever red cells transfusion is considered, and it should be carried out when the patient's volume status is clinically normal as assessed by senior clinicians. The initial score is 6, and the final score is the sum of all points plus 6, that is 6, 7, 8, 9, 10, or >10. As shown in table 1, a patient will get 1 point if his adrenaline infusion rate is ≤0.05 μg/kg/min, and 2 points if the adrenaline infusion rate is ≥0.06 μg/kg/min. If his fraction of inspired oxygen (FiO₂) is 36-50%, he will get another 1 point and so on. The sum of all points plus 6 will be the final score. If the score is ≥10, patients will be managed as if the score is 10, which means hemoglobin level should be maintained at not less than 10 grams per deciliter. If the score is less than the instant hemoglobin level, red cells transfusion will not be necessary. If the score is more than the instant hemoglobin level, red cells should be transfused, and the volume of red cells is calculated as double of the difference of Liu's score minus the instant hemoglobin level. In China, 1 unit of red cells equals to the volume of red cells in 200 ml of whole blood, and hemoglobin level could be increased 1 gram per deciliter by transfusion of 2 units of red cells in most adults.

Cardiac output is reflected by adrenalin infusion rate, and is estimated clinically based on patient's hemodynamic and cardiac rhythm/rate. Patients with insufficient cardiac output would be administrated with adrenaline infusion (or equivalent conversion of other inotrope agent infusion), and the adrenaline infusion rate will be adjusted as points added in the score. For other situations, such as bradycardia, hypotension or massive hemorrhage in which vasoactive drugs may be needed temporarily (for example, atropine, ephedrine, phenylephrine or noradrenaline), these vasoactive drugs will not be included during scoring. Oxygen saturation is reflected by pulse oximetry, and if SpO₂ can not be ob-
tained or measured accurately with pulse oximetry, arterial blood gas analysis is recommended to measure the arterial oxygen saturation. Core body temperature is the index of oxygen consumption, and it may be measured at either nasopharyngeal, oropharyngeal, tympanic membrane, rectal or esophageal route. Temperature obtained by axillary route with 0.5 ℃ added can be accepted as core temperature.

Calculation of the patient's score should be based on combination of the individualized instant hemoglobin level and specific circumstances related to oxygen carrying capacity of blood. Therefore, the West China Liu's score guided transfusion strategy is an individualized transfusion strategy.

### INDIVIDUALIZED TRANSFUSION STRATEGY TRIAL

#### Hypothesis

In our previous pilot trial comparing the effect of individualized transfusion strategy and liberal transfusion strategy (8), we found 36.5% in the individualized group and 89.4% in the liberal group of patients received red cells transfusion. Besides, we found that 76.7% in 400 patients undergoing major spine surgeries received red cells transfusion under guidance of current Chinese transfusion guidelines. Based on these findings, this trial is designed to test the hypothesis that individualized transfusion strategy by application of West China Liu's Score, as compared with a restrictive transfusion strategy guided by current transfusion guidelines and a liberal transfusion strategy of 10 grams per deciliter, the widely accepted "safe" threshold, red cells transfusion requirement can be reduced without increase of mortality, post-operative complications, or the cost of hospitalization.

#### Study Design

This trial is a prospective, multicenter, randomized controlled trial that will test the superiority of individualized transfusion strategy (red cells transfusion guided by West China Liu’s Score) to restrictive or liberal transfusion strategy in terms of reducing red cells transfusion demands safely and effectively. The protocol of the trial has been registered at http://www.clinicaltrials.gov (NCT01597232) and a brief flowchart of the whole study is summarized in the figure 1. This study is conducted according to the principles outlined in the Declaration of Helsinki. This trial is investigator-initiated with grant support from Sichuan University Education Foundation (SCUEF). All investigators in participating centers are qualified through training to conduct the trial. All patients have to sign the informed consent prior to study entry.

#### Ethics

This study protocol has been first approved by the Biological-Medical Ethical Committee of West China Hospital, Sichuan University, Chengdu, Sichuan, China on 10 January 2012, and then approved by all the participating centers successively. Details of the study will be explained thoroughly to the potential subjects and (or) their legal guardian by the investigators. The signed informed consent forms must be obtained from all eligible patients before enrollment. Patients will be given at least 24 hours to consider before enrollment. Participation to the study is entirely voluntary and patients can withdraw from the study anytime. The privacy of all participants will be protected. Personal medical records will be checked only by designated investigators and inspectors, and they will not export any confidential information. Data anonymity will be applied in the whole process of data management, and all collected data will be kept and analyzed centrally at West China Hospital.

#### Patient Eligibility

Patients with intra-operative estimated blood
Figure. The Trial Algorithm.

Subjects recruitment

Yes

Inclusion criteria fulfill and No exclusion criteria

No

Excluded

Perioperative Hb<10 g/dL

Restrictive transfusion strategy group

Individualized transfusion strategy group

Liberal transfusion strategy group

Follow up for 5 years

Data analysis

Interim analysis: approximately 1880 eligible participants (for the primary outcomes)

Interventions

In the individualized-strategy group, decision for red cell transfusion trigger and target will be made in accordance with the West China Liu's score and hemoglobin level. That is, whenever the red cells transfusion is considered, Liu’s score will be calculated and compared with the instant hemoglobin level. If the score is less than the instant hemoglobin level, red cells transfusion will not be necessary. If the score is more than the instant hemoglobin level, red cells should be transfused, and the volume of red cells is calculated as double of the difference of Liu’s score minus the instant hemoglobin level.

In the restrictive-strategy group, patients will be managed according to Chinese or European guidelines (3-5) for red cells transfusion. That is, red cells transfusion is always not recommended in patients with hemoglobin level above 10 grams per deciliter, required when hemoglobin level decrease to 7 grams per deciliter, and depends on the attending physician’s judgment with evaluation of patients’ cardiopulmonary reserve and oxygen consumption. Besides, the red cells transfusion target is not stated in the guidelines and also depends on the physician’s judgment.

In the liberal-strategy group, patients will be transfused if the hemoglobin level decreases to less than 10 grams per deciliter, in order to maintain hemoglobin not less than 10 grams per deciliter during perioperative period.

Randomization

All patients recruited to the study will be collectively randomized using SAS programming (SAS Windows 9.1) by Department of Anesthesia, West China Hospital, Chengdu, Sichuan, China. The randomization will be stratified by the participating centers, and each center is allocated with 120 subjects with the ratio of 1:1:1. Study IDs are 5-digit numbers that are randomly generated and assigned into one of the three groups by SAS. Results of the group allocation will be concealed in a non-transparent envelop with only a 5-digit number on the surface. Envelops will be distributed to the centers. At each center, eligible patients enrolled in the study will be randomly assigned a study ID in the sequence according to the order of the patient recruited.

The investigators, responsible anesthesiologists, surgeons, and the research nurses will be aware of the treatment allocation. The patients, staff responsible for follow-up, and statisticians will be blinded to the treatment assignment. After discharge, all patients will be followed up by telephone calls for five years.

Outcomes

There are two primary outcomes, the incidences of red cells transfusion requirement, and combined in-hospital death for any reason and in-hospital serious complications.

In-hospital serious complications are listed as follows:

1) Cardiac events including cardiac arrest, myocardial infarction, definite diagnosis of angina pectoris, definite diagnosis of arrhythmia, heart block needing temporary or permanent pacemaker, definite diagnosis of heart failure,
acute coronary syndrome, and cardiac infection needing antibiotics or other treatment;

2) Central nervous system events including stroke, definite diagnosis of carotid or intracranial thrombosis, definite diagnosis of intracranial hemorrhage, and intracranial infection needing antibiotics or other treatment;

3) Pulmonary events including definite diagnosis of atelectasis needing treatment, tension pneumothorax, hemothorax, or hemopneumothorax needing thoracic close drainage, pulmonary edema needing treatment, bronchopleural fistula needing surgical intervention, respiratory failure needing mechanical ventilation, pulmonary embolism with definite diagnosis, and pulmonary infection needing antibiotics or other treatment;

4) Digestive system events including anastomotic fistula, bile leakage, or biloma needing surgical intervention, definite diagnosis of hepatic dysfunction or failure, and diarrhea, gastrointestinal infection, or intra-abdominal infection needing antibiotics treatment;

5) Urinary/reproductive system events including urinary tract obstruction needing surgical intervention, acute renal insufficiency needing dialysis, and urinary/reproductive infection needing antibiotics treatment;

6) Other complications including re-operation for postoperative bleeding, definite diagnosis of disseminated intravascular coagulation, disruption of wound needing surgical intervention, infection of incisional wound needing antibiotics and other treatment, and definite diagnosis of systemic inflammatory response syndrome or sepsis.

The secondary outcomes are listed as follows:

1) Incidences of in-hospital infectious complications;

2) Intensive care unit (ICU) admission rate and ICU length of stay;

3) Length of hospital stay;

4) Hemoglobin level at different time points;

5) Red cells transfusion cost and hospital admission cost;

6) Healing status of surgical incision, which is divided into grade I, II, and III. Grade I was defined as the wound healing nicely without any adverse reaction, grade II was defined as the inflammatory wound without the need of re-incision, and grade III was defined as the wound suppurated with the need of re-incision for clearance;

7) Post-operative quality of life, which is evaluated by the 8-item Short-Form Health Survey (SF-8);

8) Death for any reason within one and five year postoperatively.

Data Collection

All patients’ demographic information, diagnoses, interventions, and in hospital serious complications and mortality will be captured from electronic hospital medical records and recorded in the paper version of case report forms. The collected data will be uploaded to electronic case report forms at www.pottstrial.com within seven days after discharge. The follow-up information will be uploaded to this website within three days after each follow-up.

Sample Size and Statistical Analysis

Our primary hypothesis is that the individualized transfusion strategy will reduce the red cells transfusion demand (incidences of red cells transfusion requirement) while do not increase the adverse events (in hospital serious complications and death rate for any reason) compared

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**Table 2. Eligibility Criteria for the Trial.**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>Age ≥ 14 years old</td>
<td>Declined to receive blood transfusion</td>
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<tr>
<td>Live in an area of altitude &lt; 2500 meters most of their lifetime</td>
<td>Refuse to sign consent</td>
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<tr>
<td>American Society of Anesthesiologists (ASA) physical status I, II, III or IV</td>
<td>Patients with physical status of ASA class V or above</td>
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<td>Undergoing elective surgery with estimated blood loss more than 1000 ml or 20% of the patient’s whole blood volume</td>
<td>Patients with known severe haematological disorders</td>
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<td>Glasgow Coma Scale (GCS) score of 15</td>
<td>Patients with known haemoglobinopathy</td>
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<tr>
<td>Ability to communicate by telephone call</td>
<td>Acute hypervolemic haemodilution is planned</td>
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<td>Informed consent has been signed by the patient or his legal guardian</td>
<td>Pregnancy</td>
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<tr>
<td>Other conditions that may preclude the patients from the study, such as language barrier, psychiatric disorders, unable to attend research center for follow up</td>
<td>Patients enrolled in another research study or are taking experimental medication in the last 3 months prior to this study</td>
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<tr>
<td>Not suitable for the study, after assessment by the investigators</td>
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to restrictive transfusion strategy. To control the overall Type I error rate under 0.05, we set the Type I error rate to be 0.025 for sample size calculation for each of the two primary hypotheses two-sided testing. We also set the power to be 90% for each outcome.

In our pilot study comparing transfusion guided by individualized and liberal transfusion strategy, we found that among 191 of patients, 36.5% in the individualized group and 89.4% in the liberal group (P<0.001) received red cells transfusion in perioperative period, and a median of zero units of red cells were transfused in the individualized group and 3.5 units in the liberal group (P<0.001) (8). Besides, we sampled 400 records of blood transfusion in spine surgeries with blood loss more than 800 ml from 2006 to 2009 in West China Hospital, Sichuan University, and found that 76.7% patients received red cells transfusion and the number of transfused Red cells units was 2.7 U on average. Therefore, it is reasonable to assume a 36.5% and 76.7% rate (difference of proportions 40.2%) for red cells transfusion requirements for the individualized strategy and the restrictive strategy group. We conservatively assume a 20% difference between the two groups (36.5% vs 56.5%). Using Z-test, we will need 153 patients in each group to detect a significant between group difference in the primary outcome of the proportion of patients who received red cells transfusion with a 90% power. Considering an estimated 20% dropout rate, 192 patients in each group are required for evaluate this primary outcome in this study. We plan to recruit 400 patients in each group for the study which will achieve a higher than 99% power. For the combined in-hospital death for any reason and in-hospital serious complications outcome, in a pilot study conducted at West China hospital, we observed rates of 6.6% and 7.9% in the individualized strategy and the restrictive strategy groups, respectively. Assuming a similar difference in this study, with 360 patients in each group to finish study, we will have a greater than 95% power to detect a significant difference between the two groups in the combined in-hospital death and serious complication rates. The power analysis is based on a two-sample Chi-square test of proportions. The analysis using Mantel-Haenszel test accommodating the center difference will be more powerful. In addition, according to the incidences of secondary outcomes and death rates for any reason within one year post-operatively, we consider a difference of 2% (e.g. 4% vs. 6%) within groups to be clinically important, with an estimated 20% dropout rate, and 4050 patients are required.

A total of 4050 patients will be enrolled at 35 centers in China, adding 150 patients for potential subjects loss due to various reasons. Two formal interim analysis will be performed when the number of enrolled patients reaches approximately 1080 for the primary outcomes of red cells transfusion requirement and combined in-hospital mortality and serious complications. Quality and validity check on all collected data, data merge across the 35 centers, and data analysis will be performed by professional statisticians at West China Hospital. All primary and secondary outcomes will be analyzed on an intent-to-treat basis using SAS 9.4 (Cary, NC). Data distribution will be checked using Kolmogorov-Smirnov goodness of fit test and homogeneity will be checked using C-variances test. Summary variables will be expressed as mean ± standard deviation (with normal distribution) or median and interquartile range (for skewed distribution). Quantitative data will be compared using an analysis of variance (ANOVA) among three groups, and t-test for comparison between two groups. For primary outcomes, transfusion rates and the in-hospital combined complications and death rates between the individualized strategy and the restrictive strategy groups, we will use Cochran-Mantel-Haenszel test for comparison, and data with skewed distribution will be analyzed using Mann-Whitney U test. A P value<0.025 is considered significant.

Study Organization
The principal investigator, a study coordinator, and the Office of Scientific Research at West China Hospital are jointly responsible for all aspects of the study protocol and amendments. Dr. Ren Liao, associate professor of Department of Anesthesiology, West China Hospital, will be responsible for site monitoring. Data collection and follow-up will be performed by three dedicated affiliated research nurses. Designated trial
monitors will review all investigational data for accuracy and completeness to ensure protocol compliance periodically.

**Study Status**

The study is currently in the process of recruiting participants in all the trial centers.

## DISCUSSION

Approximately 85 million red cells are transfused annually worldwide (9), but transfusion practices vary widely. Decision of red cells transfusion is most commonly based on the hemoglobin concentration clinically (10). According to three large randomized controlled trials (RCT) examining the effects of blood transfusion on clinical outcomes (11-13), a restrictive transfusion strategy (transfusion threshold as 7 grams per deciliter or 8 grams per deciliter), as compared with a liberal strategy (transfusion threshold as 9 grams per deciliter or 10 grams per deciliter), can decrease transfusion requirements without increasing rates of death, in-hospital morbidity, or adverse outcomes in critically ill adult patients, stable critically ill children, and elderly patients at high cardiovascular risk. As a consequence, a restrictive transfusion strategy that uses transfusion threshold of 7 grams per deciliter or 8 grams per deciliter has been recommended in most guidelines (3-5, 14). However, another RCT involving 2003 patients undergoing nonemergency cardiac surgeries demonstrated that there were more deaths in the restrictive-threshold group when compared with the liberal-threshold group (4.2% vs. 2.6%; hazard ratio, 1.64; 95% confidence interval [CI], 1.00 to 2.67; P=0.045), and the total costs did not differ significantly between the groups (15). A conclusion that restrictive transfusion threshold after cardiac surgery was not superior to a liberal threshold with respect to morbidity or health care costs was drawn from this trial. The discrepancy of these trials suggests that decision of red cells transfusion should not be made according to a fixed hemoglobin level alone, and individual circumstances should also be evaluated at the same time. Moreover, the transfusion guidelines suggest that transfusion should be considered for the risk of complications of inadequate oxygenation (3-5, 14, 16). However, these guidelines do not tell us specifically how to combine the hemoglobin level and individual patient factors to decide whether to give patients red cells transfusion, or the target hemoglobin concentration of transfusion. Besides, it remains a question whether these guidelines are suitable to guide perioperative transfusion on most ASA physical status I, II or III patients undergoing major surgeries by using the conclusions of the trials on patients with ASA physical status IV or above such as critically ill adult and pediatric patients, and geriatric patients with high cardiovascular risk. Therefore, it is vital to develop an individualized transfusion strategy for perioperative surgical patients.

We designed the West China Liu’s score as an individualized transfusion strategy for patient’s red cells transfusion trigger and target during perioperative period, and we hope this semi-quantitative score could be applied by any physician who will make the decision of red cells transfusion without complicated measurement of cardiac output, or oxygen consumption to evaluate a patient’s O2 D/C status. In this study, we will investigate whether the individualized transfusion strategy, when compared with the restrictive transfusion strategy and the liberal transfusion strategy, will decrease the red cells transfusion requirement without increasing mortality or adverse outcomes.

In conclusion, the WCPTS trial plans to investigate the efficacy and safety of the individualized red cells transfusion strategy by application of West China Liu’s Score in patients undergoing major surgery with anticipative massive blood loss. This study may provide a new insight on the perioperative transfusion and new clinical proof for the transfusion guidelines.

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