A randomised controlled trial of standard transfusion versus fresher red blood cell use in intensive care (TRANSFUSE): protocol and statistical analysis plan

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Red blood cell (RBC) transfusion is common in intensive care unit patients, and up to 70% of patients are anaemic by Day 3 of their ICU stay.[1,2] Between 20% and 40% of ICU patients receive a transfusion,[1,3-5] with reported means of 2–4.8 RBC units transfused per patient.[3,5,6] RBC transfusions are potentially life-saving for individual patients, but they have been associated with an increased risk of morbidity and mortality in critically ill, surgical and trauma populations.[7-11]

Studies have increasingly focused on potentially harmful effects of changes in RBCs with increasing storage time; effects that are likely to be due to "RBC storage lesion".[12,13] Usual practice is to issue oldest compatible RBCs to minimise expiry and wastage. Observational studies in critically ill patients have reported the association of transfusing older RBCs with mortality.[4,5,8]

To date, four randomised controlled trials (RCTs) of RBC age in adult, critically ill patients have been published, and a fifth RCT in neonates has been published. In adults, three trials were small pilot studies[14-16] and the fourth chose change in pulmonary gas exchange as the primary end point.[17] The largest RCT conducted in 277 premature neonates found no benefit for fresher (< 7 days old) RBC transfusions.[18]

The impact of RBC storage on clinical outcomes in adult, critically ill patients remains uncertain. Adequately powered RCTs are needed to determine if the observed statistical associations in critically ill patients are causal. Several large-scale RCTs are under way, and a summary of their salient features is shown in Table 1.

The Standard Issue Transfusion versus Fresher Red Blood Cell Use in Intensive Care (TRANSFUSE) trial aims to determine, in critically ill patients who need RBCs, whether transfusion of freshest available, compatible, allogeneic RBCs reduce 90-day patient mortality, when compared with standard care. To ensure transparent and unbiased conduct of our trial, we publish our protocol and statistical analysis plan (the full study protocol is available at http://www.anzicrc.monash.org/transfuse-rct.html).

Methods

Design and registration

TRANSFUSE is a multicentre, randomised, double-blind parallel-group, controlled trial comparing transfusion of the freshest available, compatible, allogeneic RBCs with standard-issue RBCs in ICU patients. The trial is registered with clinicaltrials.gov

ABSTRACT

Objective: To determine if using freshest available rather than standard-issue red blood cells (RBCs) can reduce mortality in critically ill intensive care unit patients. Our study is the largest ongoing randomised controlled trial (RCT) of RBC age in critically ill patients and will help determine if the use of the freshest available RBCs should become standard policy for the critically ill.

Design, setting and participants: A double-blind, multicentre, Phase III RCT of 5000 adult ICU patients in Australia, New Zealand, Europe and the Middle East.

Interventions: Transfusion of the freshest available RBCs in place of standard-care RBCs until hospital discharge.

Main outcome measures: The primary outcome measure is 90-day all-cause mortality. Secondary outcome measures are time to death, 28-day and 180-day mortality, persistent organ dysfunction combined with death, days alive and free of mechanical ventilation and renal replacement therapy, bloodstream infection in the ICU, length of stay in the ICU and in hospital, proportion of patients with febrile non-haemolytic transfusion reactions, and quality of life at Day 180.

Results: A detailed statistical analysis plan with predefined subgroups and secondary analyses has been finalised before results being available, to ensure an unbiased final analysis.

Conclusions: The pragmatic protocol design has been chosen to facilitate translation of the trial results into practice. The TRANSFUSE trial will have important clinical and policy implications, regardless of the outcome.

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(NCT01638416) and the Australian New Zealand Clinical Trials Registry (ACTRN12612000453886).

Population and eligibility

We will enrol 5000 adult patients in about 60 centres in Australia and New Zealand, Europe and the Middle East. ICU patients and patients in emergency departments with planned admission to the ICU will be screened for eligibility.

Table 1. Features of large-scale randomised controlled trials of the age of RBC transfusions

	Trial			
Feature	TRANSFUSE	ABLE	RECESS	INFORM
Study population	Critically ill patients	Critically ill patients	Complex cardiac surgery patients	Hospitalised patients
Number of patients	5000	2510	1696	24 400
RBC fresh	Freshest available	≤ 7 days	≤ 10 days	Freshest available
RBC control	Standard-issue RBC	Standard-issue RBC	≥ 21 days	Standard-issue RBC
Primary outcome measure	90-day all-cause mortality	90-day all-cause mortality	Change in composite MODS	Inhospital mortality
Estimated completion	December 2015	Completed	October 2013	September 2014
Registration	NCT01638416	ISRCTN44878718	NCT00991341	ISRCTN08118744

TRANSFUSE = Standard Issue Transfusion versus Fresher Red Blood Cell Use in Intensive Care. ABLE = Age of Blood Evaluation. RECESS = Red Cell Storage Duration Study. INFORM = Informing Fresh versus Old Red Cell Management. RBC = red blood cell. MODS = multiple organ dysfunction syndrome.

The detailed inclusion and exclusion criteria are shown in Table 2. Transfusion indication, timing and number of RBC units will be determined by treating clinicians. We recommend following the current Australian critical care transfusion guidelines.[19]

Randomisation

Treatment allocation will be determined using variable block randomisation in a 1:1 ratio, stratified by study centre. Clinical staff in the ICUs will randomly allocate patients using a web-based system that will assign a unique study number. When provided with this number, hospital transfusion services allocate each patient to the appropriate treatment group according to the centre's randomisation schedule.

Treatments

Freshest available RBCs

Patients will receive the freshest available, compatible, allogeneic RBC unit in the hospital transfusion service.

Standard care

Patients will receive RBCs according to standard practice, which is generally to provide the oldest available, compatible, allogeneic RBC unit in the hospital transfusion service. After ICU discharge, patients will continue to receive RBCs according to their randomised group during the index hospital stay. If patients are readmitted to hospital and require transfusion, they will receive standard-issue RBCs.

Blinding

Study group allocation will be concealed from treating medical and nursing staff as well as from research personnel. Only transfusion service staff (located in a different part of each hospital) will have access to patient treatment allocation. In keeping with usual hospital protocols and transfusion practices, details of the RBC units including collection and expiry dates will be checked before transfusion. In the ICU, this will be performed by two nurses who are not involved in the direct care of the patient. Before starting a transfusion, one of the non-bedside ICU nurses will place the RBC unit in

Table 2. Criteria for study participation

Inclusion criteria:
- Intensive care unit patients* with an anticipated ICU stay of ≥ 24 hours, when the decision has been made by medical staff to transfuse at least one RBC unit.

Exclusion criteria:
- Age younger than 18 years
- Previous RBC transfusion during the current hospital admission (including transfusion in another hospital)
- Diagnosis of transplantation or haematological malignancy
- Pregnancy
- Cardiac surgery (coronary artery bypass grafting or uncomplicated valve surgery) during current hospital admission
- Expected to die imminently (< 24 hours)
- Treating doctor believes it is not in the best interest of the patient to be included
- Known objection to administration of human blood products
- Participation in another RBC transfusion study.

RBC = red blood cell. * Can be included while in the emergency department if the decision for patient to be admitted to the ICU has been made.

Table 3. Outcomes of study

Primary outcome:
- 90-day mortality.

Secondary outcomes:
- Time to death
- 28-day mortality
- 180-day mortality
- Persistent organ dysfunction combined with death at Day 28[31]
- Days alive and free of mechanical ventilation at Day 28
- Days alive and free of renal replacement therapy at Day 28
- Bloodstream infection in the intensive care unit
- Length of stay in the ICU and in hospital
- Proportion of patients who suffer at least one febrile non-haemolytic transfusion reaction in the ICU
- Quality of life at Day 180.[20]

Table 4. Data variables collected

Demographics:
- Identity (initials, study number, date of birth, sex, postcode)
- Blood group (A, B, O, AB; rhesus D [positive or negative])
- Alloantibodies
- Comorbidities (heart disease including angina, myocardial infarction and previous CABG; immunocompromised)
- Ethnicity (patients enrolled in New Zealand only)

Hospital data:
- Admission and discharge dates
- Discharge destination

Intensive care unit data:
- Admission and discharge dates
- APACHE III score and risk of death at ICU admission
- APACHE III diagnosis code at admission
- Current "unstable or active" heart disease (cardiac arrest, arrhythmia, cardiogenic shock, angina, acute myocardial infarction)
- SOFA score at randomisation and daily during ICU admission
- Haemoglobin level at ICU admission
- Requirement for and duration of invasive mechanical ventilation
- Requirement for and duration of renal replacement therapy
- Requirement for and duration of catecholamines
- Blood stream infection (date and pathogen)

Transfusion information:
- Haemoglobin level before transfusion episode
- Date and time of each RBC unit transfused
- Blood group (A, B, O, AB; rhesus D [positive or negative])
- Donation number (pack number)
- Fresh frozen plasma (number of units after randomisation)
- Platelets (number of units after randomisation)
- Blinding status (ie, units checked by non-bedside nurse)
- Adverse events including febrile non-haemolytic reaction

Vital status at:
- ICU discharge
- Hospital discharge
- 28 days after randomisation
- 90 days after randomisation
- 180 days after randomisation

Quality of life:
- 180-day EQ-5D score[20]

CABG = coronary artery bypass grafting. APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = Sequential Organ Failure Assessment. RBC = red blood cell. EQ = EuroQuol.

a bag with opaque panels to conceal the collection and expiry dates. For patients receiving a transfusion in the operating theatre or ward after ICU discharge, RBC unit checking will be performed according to usual practice by treating staff. A pilot study performed in preparation for the main trial showed that clinical staff remained blind to treatment group, confirming the feasibility and efficacy of these blinding procedures.[16]

For the purposes of later analysis, RBC unit collection and expiry dates will be obtained directly and sequentially from the national blood services in participating countries.

Primary and secondary outcome measures

The primary outcome will be 90-day all-cause mortality. Secondary outcome measures are shown in Table 3.

Data

Data collection

All data will be collected at each site and entered into a web database designed by the Clinical Informatics and Data Management Unit (CIDMU), Monash University, Melbourne, Australia. Patients will be followed up to death or 180 days after randomisation. Data variables, along with the collection timetable, are shown in Table 4. Data entry and management will be coordinated by the project manager and the coordinating centre, the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University, Melbourne.

### Data quality and protocol adherence

Detailed discussion and review of study procedures was undertaken at preliminary meetings with research coordinators and investigators from all sites. A data dictionary with precise definitions of all variables was provided to sites. The project manager and the CIDMU will perform timely validation of data, queries and corrections. Site visits will be made to monitor data quality on 10% of patients.

To ensure adequate treatment separation, an assessment of RBC age will be performed on a site-by-site basis after 50 patients have been enrolled at each site. In the absence of definitive evidence of the RBC age at which harmful clinical effects occur, the management committee and the data and safety monitoring committee (DSMC) reached consensus that a minimum of 7 days' treatment separation will be needed. Separation will be reviewed by the TRANSFUSE management committee, and the DSMC will be notified simultaneously. If treatment separation is less than 7 days at any site, a site visit will be instigated and site closure or capping of recruitment will be considered. The pilot study, using the same method of treatment allocation, achieved over 12 days' separation at two sites in Australia.[16]

Statistical analysis plan

Power and sample size

The study sample of 5000 patients will provide 90% power for a two-sided difference of 4.2% in the primary outcome of 90-day mortality between treatment groups. The baseline mortality was estimated from a previous observational study.[4] Patients in our study who would have been eligible for the TRANSFUSE trial had a hospital mortality of 25%. We conservatively estimate the 90-day mortality to be 28%.

The sample size calculation was based on a 15% relative decrease in 90-day mortality, or an absolute decrease of 4.2% from 28% to 23.8%. With a type I error of 0.05 and a type II error of 0.1 (power 90%), the needed patient number

Figure 1. Patient flow through study

RBC = red blood cell.
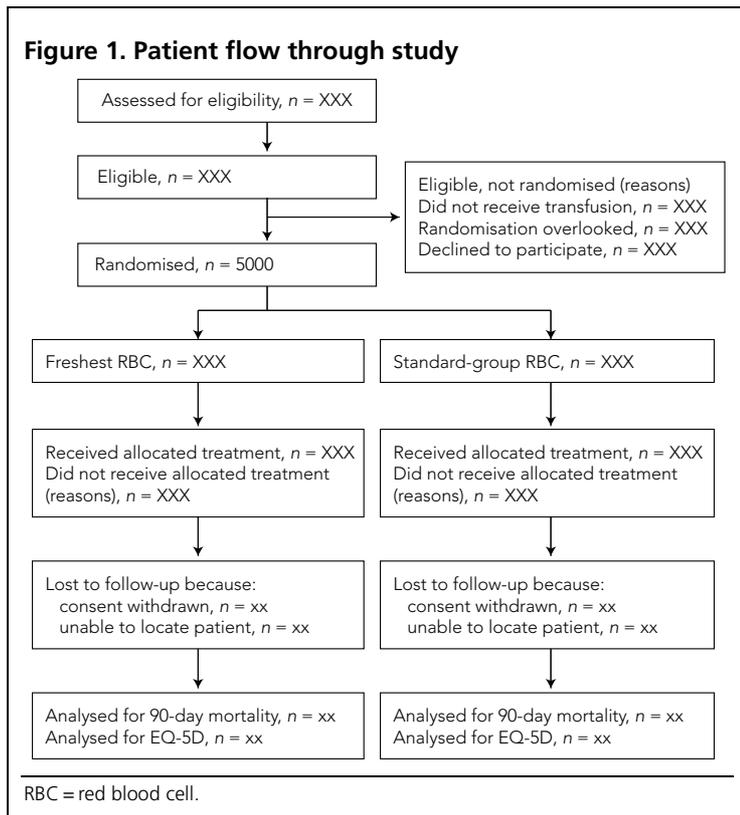
Table 5. Subgroups for analysis of primary and secondary outcomes and proposed secondary analyses to explore the relationship of age of RBC and mortality

A priori defined subgroups:
- Group O v non-group O
- Acute Physiology and Chronic Health Evaluation III risk of death < median v > median
- Baseline Sequential Organ Failure Assessment scores < median v > median

Secondary analyses to study mortality:
- RBCs < 8 days old (all units) v at least 1 unit ⩾ 8 days
- Mean RBC age quartiles
- Mean RBC age as continuous variable
- Minimum RBC age as continuous variable
- Maximum RBC age as continuous variable

RBC = red blood cell.

is 2332 per group. According to previous studies,[21,22] the loss to follow-up should not exceed 5%; the addition of 5% yields an accurate number of 4898 patients, which we have rounded up to 5000 patients.

Analytical plan

We will generate a Consolidated Standards of Reporting Trials diagram of patient flow (Figure 1).

All analyses will be on an intention-to-treat basis, except where otherwise indicated. No imputation for missing data will be performed and the number of analysed observations will be reported. The level of significance is set to 0.05 in all analyses and *P* will not be adjusted for multiplicity. All analyses will be unadjusted unless otherwise specified.

Baseline variables

We will compare baseline variables according to randomly allocated groups, and will perform comparisons using χ^2 tests for proportions, student *t* tests for continuous normally distributed variables and Wilcoxon rank-sum tests otherwise. *P* values will be reported according to publisher's requirements.

Primary outcome

We will compare 90-day all-cause mortality according to the intention-to-treat principle between treatment arms using a χ^2 test for equal proportions, and report as frequency (percentage) per arm, and as odds ratios (ORs) with 95% confidence intervals. We will perform an accessory-adjusted analysis for sensitivity purposes, using multivariable logistic regression adjusting for four variables: hospital, APACHE III risk of death, haemoglobin level at randomisation and blood group. Results will be reported as ORs with 95% CIs.

Secondary outcomes

We will analyse survival time from randomisation to Day 90 using Cox proportional hazards regression, and will report it as hazard ratios and 95% CIs. The proportional hazards assumption across treatment arms will be visually assessed using log-cumulative hazard plots. Survival results will be presented using Kaplan–Meier curves with a log-rank test for equality of survivor functions across treatment arms.

Binary secondary outcome variables (28-day mortality, persistent organ dysfunction combined with death at Day 28, blood stream infection in ICU and febrile non-haemolytic transfusion reaction) will be analysed using χ^2 tests for equal proportion and reported as frequencies (percentages) with ORs and 95% CIs.

We will calculate lengths of stay in the ICU and hospital from random allocation to discharge, with censoring at death or 90 days. We will determine treatment comparisons using a log-rank test and report them using Kaplan–Meier curves. We will also report length-of-stay variables separately for survivors and non-survivors and compare them using Wilcoxon rank-sum tests, and report results as medians with interquartile ranges (IQRs).

For efficacy outcomes (days alive and free of mechanical ventilation and renal replacement therapy at Day 28), we will present results in two ways: numbers and percentages of

patients per arm receiving the therapy, and medians and IQRs of days without these therapies.

We will report quality of life as means and SDs, or medians and IQRs, as appropriate. The effect of allocated treatment will be assessed by using the two-sample t test or the Wilcoxon rank-sum test, depending on the nature of distribution of the variable. Quality of life will also be reported as the proportion of reported problems for each of the dimensions of the questionnaire.[20] In addition, we will determine a single-index score using the United Kingdom time trade-off tariff[23] with the results presented as means and SDs or medians and IQRs, as appropriate. The proportions for each dimension will be compared with a χ^2 test, and the index scores with the two-sample t test or the Wilcoxon rank-sum test, as appropriate.

For all secondary outcomes, we will also perform adjusted analyses by adjusting for study centre, APACHE III risk of death, haemoglobin level at randomisation and blood group. ABO blood group may have an influence on the age of transfused blood, susceptibility to thromboembolism or severe infections.[24-27] We will perform the analyses using logistic regression for binomial outcomes with results reported as ORs with 95% CIs, and using Cox proportional hazards regression for time-to-event data with results reported as hazard ratios with 95% CIs. We will assess continuous outcomes for normality and, where appropriate, will perform sensitivity analysis using linear regression and reporting results as differences (or ratios, if log-transformations are needed).

Subgroup analysis

We will perform all previously described analyses for primary and secondary outcome variables separately for each subgroup. Each analysis will be accompanied by a test for interaction between treatment and subgroup to ascertain if there is statistical evidence to support the assumption that treatment effect differs significantly between subgroups. We will present subgroup results as forest plots with an accompanying P value for heterogeneity across subgroups. The patient subgroups are shown in Table 4.

Secondary analysis

We may undertake per-protocol analyses for primary and secondary outcome measures as well as for all preplanned subgroups to determine the effect (if any) of protocol violations and treatment crossover. The relationship of age of RBCs with mortality will be analysed as predefined secondary analyses (Table 5).

Safety

Data and safety monitoring committee

An independent DSMC comprising acknowledged experts in the field will conduct one planned interim safety analysis when half of the specified overall patient recruitment target (5000 patients) are enrolled, ie, when 2500 patients are enrolled. The DSMC will assess the differential proportion of all-cause mortality between the two treatment groups (a safety assessment of the trial primary outcome) as well as the differential cumulative serious adverse event (SAE) reports. The DSMC may request assessment of any other trial data at any time. The DSMC will assess the efficacy according to the Haybittle–Peto method as guidance for stopping the trial early if the difference in the primary outcome between the two groups reaches the statistical significance level of $P < 0.001$ with two-sided testing. This corresponds to a threshold treatment effect of $z = 3.0$ in standardised units.

Adverse events

We will collect records of defined adverse events as study outcomes (Table 3). Any record of undefined adverse events will be collected if considered to be causally related to the study intervention, or if otherwise considered to be of concern in the investigator's judgement.

Serious adverse events

We expect the baseline mortality of study patients to be high (equivalent to a hospital mortality of 25%). We expect that patients will frequently develop organ failure despite optimal management and unrelated to study interventions. Therefore, to be consistent with the advice of Cook and colleagues,[28] we will not report as SAEs events that are part of the natural history of the primary disease process or expected complications of critical illness in this trial. Additionally, we will not label or report separately as adverse events or SAEs events already defined and reported as study outcomes (Table 3) unless they are considered to be causally related to the study intervention or are otherwise of concern in the investigator's judgement.

Unblinding

We will blind investigators to the data until we have made final database entries, resolved final queries and locked the database. We will restrict unblinded access to data for the interim analysis to the DSMC and allow access only if requested. The statistician performing interim analyses will perform analyses in a blinded fashion. Treatment allocations will be stored securely in a separate location for that purpose.

Ethical considerations

We will perform the TRANSFUSE study according to the ethical principles of the Declaration of Helsinki Guidance on Good Clinical Practice[29,30] and National Health and Medical Research Council of Australia (NHMRC) national statement on ethical conduct in human research.[31] We will obtain approval of the protocol and related documents before beginning the study, at each site, according to each country's legislation. Many patients will not have the capacity to

consent, therefore, waiving of consent, opt-out or deferred consent procedures have been granted according to local regulations.

Funding and support

Conclusions

The TRANSFUSE trial is the largest ongoing RCT evaluating the impact of RBC age on patient outcomes in critically ill adults. Because of its large sample size and robust design, the TRANSFUSE trial will answer the question of whether fresher blood in ICU patients decreases 90-day mortality when compared with standard-issue blood. If transfusion of fresher blood is safer than current practice, implementation of new transfusion policies in ICU patients would be feasible because of the pragmatic study design. When completed, the trial will have important health policy implications worldwide, independent of the outcome.

Competing interests

None declared.

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Appendix. Management and investigation teams

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