InPUT-study

Study protocol
Version 6.0

International Point Prevalence Study of Intensive Care Unit
Transfusion Practices

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**PROTOCOL TITLE:** International Point Prevalence Study of Intensive Care Unit Transfusion Practices

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<td>Version</td>
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<td>Date</td>
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<th>Abbreviation</th>
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<tr>
<td>ABR</td>
<td>ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<td>AR</td>
<td>Adverse Reaction</td>
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<td>CA</td>
<td>Competent Authority</td>
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<td>CCMO</td>
<td>Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek</td>
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<td>CV</td>
<td>Curriculum Vitae</td>
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<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>Hb</td>
<td>Hemoglobin</td>
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<td>Investigator’s Brochure</td>
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<td>IC</td>
<td>Informed Consent</td>
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<td>ICU</td>
<td>Intensive care unit</td>
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<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<td>IMPD</td>
<td>Investigational Medicinal Product Dossier</td>
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<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>METC</td>
<td>Medical Research Ethics Committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie (METC)</td>
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<tr>
<td>(S)AE</td>
<td>(Serious) Adverse Event</td>
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<td>Sponsor</td>
<td>The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.</td>
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<tr>
<td>Wbp</td>
<td>Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)</td>
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<td>WMO</td>
<td>Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)</td>
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SUMMARY

Rationale: Since a transfusion guideline specific for intensive care patients is currently lacking, we expect a large heterogeneity in transfusion practice worldwide.

Objective: Quantifying current transfusion practice in intensive care units (ICUs) and investigate differences in transfusion practice between and within different world regions (Europe, America and Asia).

Study design: International multicentre prospective observational point prevalence study. All patients admitted during one week will be included and followed for 28 days. Data regarding general demographic, admission data and transfusion triggers (haemoglobin level, platelet count, PT, APTT, INR, clinical indication) will be collected. For transfused patients and for non-transfused patients the nadir value of transfusion triggers will be collected. Transfusion products (red cell concentrates, plasma, platelets, fibrinogen and co-fact) will be recorded per amount and type.

Study population: Patients admitted to the ICU, 18 years or older.

Main study parameters/endpoints: The number of transfusion products per patient in relation to transfusion triggers. Differences within and between regions will be studied. Secondary outcomes are 28-day mortality and ICU length of stay in relation to transfusion strategy.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This study is a descriptive study and only includes objective data collected as part of routine care. No intervention takes place. Therefore, this study does not result in any risk or burdens to patients.
1. INTRODUCTION AND RATIONALE

1.1 Introduction
Anaemia, thrombocytopenia and coagulopathy are common life threatening issues in intensive care unit (ICU) patients and are correlated with mortality and morbidity\(^1\)\(^-\)\(^4\). Although transfusion of blood products can be lifesaving, it might also be associated with serious adverse effects including infections and multi-organ failure\(^5\)\(^,\)\(^6\).

During the last decades more awareness has been raised concerning the side effects of transfusion. Since the equivalence of a restrictive and liberal transfusion strategy for red blood cells was proven\(^7\)\(^-\)\(^10\), the transfusion practice of red blood cells has been shifted from a liberal to a more restrictive strategy\(^11\)\(^,\)\(^12\). Guidelines are now recommending a haemoglobin threshold of \(<7\text{ g/dl}\) in most of ICU patients. Unfortunately the optimal transfusion strategy still remains debatable for several subpopulation such as patients older than 65 years and patients with acute coronary syndrome\(^13\)\(^,\)\(^14\). Furthermore, guidelines specific for ICU patients are lacking. This discussion regarding the optimal transfusion strategy does not only apply to red blood cell products, but also concerns platelets, plasma and other coagulation factors. Where multiple large randomized trials have been performed regarding red blood cell transfusion, evidence for the optimal transfusion strategy for platelets and plasma is more limited, especially in the intensive care setting. As a result heterogeneous transfusion practice exists for these products as is shown in a study performed in the UK 2011\(^15\). This study showed an inconsistent transfusion practice regarding indications and number of transfused units of plasma. In addition, the benefit of a large amount of the transfused plasma units has never been proven\(^15\). Another study performed in Australia showed similar results, about 27-51\% of all plasma transfusion were given without a proper indication\(^16\). The same holds true for platelet transfusion, 29-51\% of all platelet transfusions in South-Wales Australia were transfused without a reasonable indication\(^17\). Due to the complexity and heterogeneity of the ICU patient population, current guidelines such as the NICE are not always applicable to critically ill patients\(^18\). At current, an ESICM taskforce is preparing specific blood component transfusion guidelines for the intensive care setting. It will be useful to determine current transfusion practice which can be compared in a few years after implementing this new guideline. This study aims to give an overview in current transfusion practice on the ICU worldwide. This information might help improve future guidelines, patient care and set new goals for research.

1.2 Relevance
Transfusion practice has already been studied before on the ICU and the operating theater\(^17\)\(^,\)\(^19\)\(^-\)\(^21\). However, these studies were held in a limited number of hospitals within the same country, were limited to only one type of transfusion, are often outdated and difficult generalizable to other hospitals and regions. Since these large observational studies, numerous of randomized controlled trials on RBC transfusion have been published supporting the safety of more restrictive transfusion strategy\(^7\)\(^-\)\(^10\). However, current
transfusion practice remains unknown. There is a need 1) to describe current transfusion practice for RBC but also for other blood components and coagulation factors, 2) to identify area of improvement, 3) to have large observational data to generate hypotheses on optimal transfusion triggers in subgroups of critically ill patients including patients with brain injury, cardiovascular diseases and elderly patients.

This study will be the first worldwide transfusion practice point prevalence trial on the ICU, which studies the practice of administration of different blood products and coagulation factors.
OBJECTIVES

Primary Objective:
- Number of red blood cell, platelet, and coagulation factors in correlation to haemoglobin levels, platelet count and INR (or PT) respectively.

Secondary Objectives:
- To evaluate which other triggers such as hemodynamic or comorbidities influence RBC transfusion practice.
- To compare haemoglobin levels in transfused patients with nadir levels of haemoglobin in non-transfused patients
- To compare platelet count in transfused patients with platelet to nadir platelet count in non-transfused patients
- To compare INR (or PT) in transfused patients with plasma to nadir level of INR(PT) in non-transfused patients
- To compare transfusion practice between different subgroups of patients including shock septic, haematology, cardiovascular disease without acute coronary diseases and coronary disease
- Association between restrictive and liberal RBC transfusion strategy on ICU length of stay and 28-day mortality
- Association between restrictive and liberal platelet transfusion strategy on ICU length of stay and 28-day mortality
- Association between restrictive and liberal coagulation factor suppletion strategy on ICU length of stay and 28-day mortality
2. STUDY DESIGN
This study is a prospective, descriptive study and only includes objective data collected as part of routine care. No intervention takes place. ICUs in different world regions will be asked to participate in this study. Each centre can choose a week to participate from several pre-specified weeks. All newly admitted patients on the ICU in that specific week will be included and followed until discharge and/or 28 days (see Figure 1 for study flow).

A transfusion event is defined as the administration of a blood derived product or coagulation factor with as aim to treat or prevent anaemia, bleeding and/or coagulopathy. This includes administration of red cell concentrates, platelet concentrates, plasma and coagulation factors including fibrinogen concentrate, cryoprecipitate and prothrombin complex. For each transfusion event data will be collected prospectively using a questionnaire on prescription behaviour. Also transfusions administered on the operating theatre while admitted to the ICU will be included for analysis.

The daily questionnaire contains clinical and laboratory data. These data include nadir haemoglobin levels, platelet count and INR or PT. This data will be necessary to compare data between patients who did receive a transfusion to patients who did not receive transfusions. Furthermore, information about 24h fluid balance and anticoagulants administration will be collected. Finally after 28 days patient outcome data: length of ICU stay and 28-day mortality will be collected.

STUDY POPULATION

2.1 Population
All newly admitted patients on the ICU in a pre-specified week (7 days).

2.2 Inclusion criteria
All patients admitted to the ICU in a pre-specified week.

2.3 Exclusion criteria
Patients younger than 18 years old.

2.4 Sample size calculation
It is planned to recruit 10 000 patients. The CRIT study and European data reported RBC transfusion rate of 30 to 40% for patients during their stay on the ICU. Furthermore, transfusion rates for platelet concentrates and plasma of 12% and 9% have been reported. However, in this study we will include all transfusion events during a pre-specified week and day. Depending on the study design, it is estimated that approximately 10-20% of all patients will receive at least one blood product, resulting in a total of approximately 1000-2000 transfusion events. As for the primary outcome merely descriptive statistics will be used, this will be a sufficient number of transfusion events. This is in accordance with data available from the most recent study investigating transfusion practices worldwide, in which 10.069 patients were included.
2.5 Sub group analyses

If sufficient number of patients and transfusions are included, transfusion regimen in different subpopulations will be analysed:

- Patients >75 years
- Patients with acute coronary syndrome
- Patients with cardiovascular diseases other than acute coronary syndrome
- Patients post cardiothoracic surgery
- Patients with traumatic brain injury
- Patients with septic shock
- Haematology patients
- Oncology patients
- Patients with ARDS
- Patients on ECMO
3. METHODS

3.1 Study parameters/endpoints

3.1.1 Main study parameter/endpoint
Main study aim is to describe current transfusion practice. This includes number of transfused units of red blood cells concentrates, platelet concentrates, plasma, cryoprecipitate when available and products that are not blood components but that derived from blood and that include coagulations factors such as prothrombin complex, fibrinogen or tranexamic acid per patient. This will be correlated with haemoglobin levels, platelet count, INR (or PT), fibrinogen prior to transfusion.

3.1.2 Secondary study parameters/endpoints
Secondary parameters will be:
- Mortality and length of stay in the ICU.
- Differences of transfusion regimes between world regions
- Differences of transfusion practices between different patient subgroups

3.2 Data collection
All newly admitted patients at the ICU older than 18 years will be included for seven consecutive days. At the start, baseline characteristics will be scored prospectively. Also, patients will be scored daily using daily questionnaires until discharge with a maximum of 28 days. At the day 28, patient outcomes are scored irrespective whether they were discharged. Furthermore, for each transfusion event or administration of coagulations factors a questionnaire will be filled in. See Figure 1 for the workflow.
The following data will be collected:

**Baseline characteristics:**
- Demographics
- SOFA score at inclusion
- Type of admission
- Presence or absence and the type of shock on the study day
- Heart rate, systolic and diastolic blood pressure
- Ventilator settings
- Renal replacement therapy during that day

**Questionnaire per transfusion event:**
- General
  - Active bleeding
  - Bleeding control
- Red cell transfusion
  - Haemoglobin(Hb)/haematocrit (Ht) level
    - Hb threshold for this patient
    - Presence of physiological trigger, and which trigger has been used.
    - Transfusion relevant comorbidity

**Figure 1. Workflow InPUT study**

The following data will be collected:
- **Platelet transfusion**
  - Platelet count prior to transfusion
  - Platelet count threshold for transfusion for this patient
  - Type of Platelet concentrate
  - Anticoagulant usage the past 72 hours
  - Usage of point of care to assess blood coagulation: ROTEM or multiplate
  - Number of units transfused
  - Upcoming procedures

- **Plasma**
  - INR prior to transfusion
  - Anticoagulant usage the past 72 hours
  - Usage of point of care to assess blood coagulation
  - Amount of plasma transfused
  - Upcoming procedures

- **Prothrombin complex concentrate (i.e. Cofact ®).**
  - INR or PT
  - Dosage of prothrombin complex concentrate
  - Usage of point of care to assess blood coagulation
  - Upcoming procedures

- **Massive transfusion protocol:**
  - Lowest haemoglobin level
  - Lowest platelet count
  - INR
  - Usage of point of care to assess blood coagulation
  - Number of Red blood cell units transfused
  - Number of platelet concentrate units transfused
  - Amount of plasma transfused
  - Tranexamic acid, fibrinogen, rFactor VIIa, Cryoprecipitate, factor XIII, aprotinin, novoseven (=eptacog alfa)
  - Bleeding control

**Daily questionnaire**

- Estimated blood loss
- Total number of transfused RBCs
- Total number of transfused platelet concentrates
- Total ml transfused plasma
- Volume administration in 24 hours
- Lowest haemoglobin level, lowest platelet count, highest INR in 24 hours
- Tranexamic acid administration in 24 hours
- Transfusion within 24 hours outside the ICU (e.g. on operating theatre)

At day 28
- 28-day mortality
- Length of stay on ICU
- Iron administration within ICU admission

3.3 Withdrawal of individual subjects
Apart from withdrawal of consent, subjects will not be withdrawn from the trial. In case of withdrawal, the data collection will be stopped and subject will not be replaced.

3.4 Replacement of individual subjects after withdrawal
Subjects will not be replaced in case of withdrawal.

3.5 Follow-up of subjects withdrawn from treatment
Not applicable

3.6 Premature termination of the study
Since this is an observational study, no interim analysis is planned. Therefore there are no criteria that are defined for premature termination of the study.

3.7 Feasibility
The feasibility of this protocol was shown in a pilot study. Based on this pilot, the protocol was adjusted. Time consuming data collection that did not result in reliable and useful information was removed from the study protocol, including daily fluid balance and additional questions for the non-transfused patients. Also the workflow of the data collection was improved using an electronic CRF. We expect this to reduce the amount of time to complete the different forms. Also obtaining informed consent will not be necessary in every centre depending on national and local regulations for observational research.
4. SAFETY REPORTING

4.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.
5. STATISTICAL ANALYSIS

5.1 Primary study parameter(s)

This is a descriptive study. Only descriptive statistical methods will be used for the primary endpoint. Continuous normally distributed variables will be expressed by their mean and standard deviation or when not normally distributed as medians and their interquartile ranges. Categorical variables will be expressed as n (%).

5.2 Secondary study parameter(s)

Data obtained during this study will be checked for distribution. Normal data will be analysed using ANOVA analysis or student t-test. Non-parametric data will be analysed with Mann Whitney U-test or Kruskall wallis. Categorical data will be compared using chisquare or Fisher’s exact test. A logistic regression model will be performed to assess independent association between number of transfusions and outcome (mortality and ICU length of stay). Results of the logistic regression will be reported as adjusted odds ratio (OR) with 95% confidence intervals.

If a sufficient number of patients can be included, propensity score matching for a liberal and a restrictive transfusion regime will be performed for each type of product. The criteria for a liberal an restrictive transfusion regime for red blood cells, platelets and plasma will be determined during the study. A p-value <0.05 will be considered to be significant.
6. ETHICAL CONSIDERATIONS

6.1 Regulation statement
This trial will be conducted according to the principles of the Declaration of Helsinki as stated in the current version of Fortaleza, Brazil, 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO).

6.2 Recruitment and consent
Since the proposed study is an observational study, no research related interventions will take place. Therefore, no ethical concerns exist. Institutional review board approval will be obtained by the participating institutions according to local ethical regulations. If a waiver is not granted informed consent forms and written patient information will be provided by the sponsor.

6.3 Benefits and risks assessment, group relatedness
This study is a descriptive study and only includes objective data collected as part of routine care. No intervention takes place. Therefore, this study does not result in any risk or burdens to patients

6.4 Compensation for injury
The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. However, as this study is an observational study, an exception from the requirement for insurance to cover for damage to research subjects through injury or death caused by the study is applicable.

7. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

7.1 Handling and storage of data and documents
Subject data will be stored anonymously using a coding system. The codebook will be stored digitally and in paper. The paper version will be stored behind a lock and the digital form will be encrypted with a double password. All data will be stored for the length of the study and for 15 years afterwards. All handling of personal data will comply with the European General Data Protection Regulation act.

7.2 Quality Assurance
The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented and reported in compliance with the protocol and regulatory requirements. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.
7.3 Public disclosure and publication policy
We are free to make a publication and have no restrictions made by a sponsor.

8. TIMELINE

April 2018: Writing study protocol
January-February 2019: Pilot study in Amsterdam testing feasibility
April 2018-December 2019: Recruiting Centers
August 2019-May 2020: Obtaining approval from institutional review boards for each country
March 2020: Start data collection
February 2021: Data analysis
March 2021: Writing manuscript
9. REFERENCES


guiding allogeneic red blood cell transfusion. 5–7 (2012).
doi:10.1002/14651858.CD002042.pub3.Copyright


