Supplementary Material

This supplementary has been provided by the authors to give readers additional information about their work.

Supplement to: CT Anthon, F Pène, A Perner et al. Platelet transfusions and thrombocytopenia in intensive care units: protocol for an international inception cohort study (PLOT-ICU)
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Supplement 1 (S1): Strengthening the reporting of observational studies in Epidemiology (STROBE) statement

STROBE Statement—Checklist of items that should be included in reports of cohort studies

| Item No | Recommendation                                                                 | Page No |
|---------|---------------------------------------------------------------------------------|---------|
| **Title and abstract** 1 | *(a) Indicate the study’s design with a commonly used term in the title or the abstract* *(b) Provide in the abstract an informative and balanced summary of what was done and what was found* | 1, 3    |
| **Introduction** 2   | Explain the scientific background and rationale for the investigation being reported | 4       |
| **Objectives** 3    | State specific objectives, including any prespecified hypotheses                | 5       |
| **Methods** 4       | Present key elements of study design early in the paper                          | 6       |
| **Study design** 4  | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6-9, Figure 1. |
| **Setting** 5       | *(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up* *(b) For matched studies, give matching criteria and number of exposed and unexposed* | 6-7, 9  |
| **Participants** 6  | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-8 and supplement 9-10 |
| **Variables** 7     | For each variable of interest, give sources of data and details of methods of assessment (measurement). | 8       |
| **Data sources/measurement** 8* | |
| Section                      | Requirement |
|------------------------------|-------------|
| Describe comparability of assessment methods if there is more than one group | NA          |
| Bias                         | 9           | Describe any efforts to address potential sources of bias | 10-12 |
| Study size                   | 10          | Explain how the study size was arrived at                 | 9     |
| Quantitative variables       | 11          | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 10     |
| Statistical methods          | 12          | (a) Describe all statistical methods, including those used to control for confounding | 10-12 |
|                              |             | (b) Describe any methods used to examine subgroups and interactions |
|                              |             | (c) Explain how missing data were addressed |
|                              |             | (d) If applicable, explain how loss to follow-up was addressed |
|                              |             | (e) Describe any sensitivity analyses |
| Results                      |             |                                                         |
| Participants                 | 13*         | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | NA    |
|                              |             | (b) Give reasons for non-participation at each stage |
|                              |             | (c) Consider use of a flow diagram |
| Descriptive data             | 14*         | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | NA    |
|                              |             | (b) Indicate number of participants with missing data for each variable of interest |
|                              |             | (c) Summarise follow-up time (eg, average and total amount) |
| Outcome data                 | 15*         | Report numbers of outcome events or summary measures over time | NA    |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included.  
(b) Report category boundaries when continuous variables were categorized.  
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses. |
| Discussion |  | |
| Key results | 18 | Summarise key results with reference to study objectives. |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results. |
| Other information |  | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.
Supplement 2 (S2): PLOT-ICU Investigators and sites

Planned sites and investigators at the protocol stage. More will be added during the study.

| Country (n) | Site                                                                 | Main investigator(s)          |
|------------|----------------------------------------------------------------------|-------------------------------|
| Denmark (10) | Department of Intensive Care, Rigshospitalet, University of Copenhagen, Copenhagen | Carl Thomas Anthon        |
|            | Departments of Intensive Care, Zealand University Hospital, Koege and Roskilde | Thomas Hildebrandt          |
|            | Department of Anaesthesiology and Intensive Care, Holbaek Hospital, Holbaek | Mette Kragh Vogelius         |
|            | Department of Intensive Care, Bispebjerg Hospital, Copenhagen.         | Niels Clausen                |
|            | Department of Anaesthesia and Intensive Care, Copenhagen University Hospital, North Zealand, Hilleroed | Morten Bestle                |
|            | Department of Anaesthesia and Intensive Care, Copenhagen University Hospital, Herlev-Gentofte Hospital, Herlev | Kristian Lorentzen         |
|            | Department of Intensive Care, Odense University Hospital, Odense       | Lene Bjerregaard Nielsen     |
|            | Department of Anaesthesiology and Intensive Care, Aalborg University Hospital, Aalborg | Jo Bønding Andreasen      |
|            | Department of Anaesthesiology and Intensive Care, Aarhus University Hospital, Aarhus | Christine Lodberg Hvas     |
|            | Department of Anaesthesia and Intensive Care, Copenhagen University Hospital - Amager and Hvidovre, Hvidovre. | Christian Svendsen Juhl |
| Sweden (2) | Department of Intensive and Perioperative Care, Skåne University Hospital, Lund and Malmö | Linda Lundqvist            |
|            | Department of Intensive Care, Södersjukhuset, Stockholm               | Elin Lindquist              |
| Norway (6) | Department of Anaesthesia and Intensive Care Medicine, Division of Emergencies and Critical Care, Rikshospitalet, Oslo University Hospital, Oslo | Andreas Barratt-Due          |
|            | Department of Anaesthesia and Intensive Care, Oslo University Hospital, Akershus, Oslo | Per Martin Bådstøøkken     |
|            | Department of Intensive Care, Oslo University Hospital, Ullevål, Olso | Aleksander Rygh Holten     |
|            | Department of Intensive Care, Haukeland University Hospital, Bergen | Reidar Kvåle                |
|            | Department of Intensive Care, Stavanger University Hospital, Stavanger | Kristian Strand            |
|            | Department of Intensive Care, Trondheim University Hospital, Trondheim | Pål Klepstad               |
| Finland (3) | Department of Anaesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki | Johanna Hästbacka        |
|            | Department of Intensive Care, Tampere University Hospital. Tampere    | Ville Jalkanen              |
| Country       | Department                                                                 | Authors                                      |
|--------------|----------------------------------------------------------------------------|----------------------------------------------|
| Finland      | Department of Intensive Care, Kuopio University Hospital, Kuopio            | Matti Reinikainen                            |
| France (10)  | Medical ICU, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris (AP-HP), Paris, France | Edwige Péju, Nathalie Marin, Frédéric Pène     |
|              | Department of Intensive Care, Hôpital Necker AP-HP, Paris, France          | Damien Vimpere                               |
|              | Medical ICU, Hôpital Pitié Salpêtrière AP-HP, Paris                        | Sophie Menat                                 |
|              | Medical ICU, Hôpital Tenon AP-HP, Paris                                    | Guillaume Voiriot                            |
|              | Medical ICU, Hôpital Avicenne AP-HP, Paris                                 | Julien Schmidt                              |
|              | Medical ICU, Hôpital Henri Mondor AP-HP, Paris                             | Etienne Dufranc                             |
|              | Medical ICU, Hôpital Louis Mourier, AP-HP, Paris, France                   | Fabrice Uhel                                |
|              | Medical ICU, Hôpital Saint-Louis, APHP, Paris, France                      | Antoine Lafarge                             |
|              | Medical ICU, Hôpital Saint-Antoine AP-HP, Paris                            | Louai Missri, Hafid Ait-Oufella              |
|              | Medical ICU, CHU de Nantes, Nantes                                        | Emmanuel Canet                              |
| United       | Department of Critical Care, King’s College Hospital NHS Foundation Trust, London, United Kingdom | Victoria Metexa                              |
| Kingdom (3)  | Department of Intensive Care, Glasgow Royal Infirmary, Glasgow, Scotland   | Kathryn Puxty                               |
|              | Department of Intensive Care, Queen Elizabeth University Hospital, Edinburgh, Scotland | Christopher Wright                          |
| Spain (1)    | Medical Intensive Care Unit, Hospital Clinic of Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain | Pedro Castro                                |
| Portugal (5) | Department of Intensive Care, Hospital Prof Doutor Fernando Fonseca, Amadora, Lisbon | Carolina Costa                              |
|              | Polyvalent Intensive Care Unit, São Francisco Xavier Hospital, Sao Francisco Xavier Hospital, CHLO, Lisbon | Luis Coelho, Pedro Povoa                    |
|              | Department of Intensive Care, Hospital da Luz, Lisbon,                     | Maria Carolina Paulino                      |
|              | Department of Intensive Care, Centro Hospitalar do Funchal, Madeira        | Carina Graça                                |
|              | Medical ICU, Hospital Egas Moniz – Centro Hospitalar Lisboa Ocidental, Lisbon | João Carlos Sousa Torres                    |
| USA (2)      | Critical Care Medicine Service, Department of Anesthesiology & Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, | Sanjay Chawla, Louis Voigt                   |
|              | Division of Pulmonary and Critical Care, Penn State University College of Medicine, Hershey, PA | Andry Van de Louw                           |
| Canada (1)   | Interdepartmental Division of Critical Care Medicine, Department of Medicine, Mount Sinai Hospital/University Health Network, Toronto, Ontario. | Laveena Munshi                              |
| Germany (3) | Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover | Catherina Lueck |
| --- | --- | --- |
| Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. | Matthias Kochanek |
| Department of Hematology and Stem Cell Transplantation, University Hospital Essen, University of Duisburg-Essen, Essen, Germany | Tobias Liebgrets |
Supplement 3 (S3): Steering and management committees

**Steering committee:**

Elie Azoulay, MD PhD  
Médecine Intensive et Réanimation  
Hôpital Saint-Louis, APHP  
Faculté de Médecine Université Paris Cité Descartes  
France  
Frédéric Pène, MD, PhD  
Médecine Intensive et Réanimation  
Hôpital Cochin, AP-HP, Paris  
Faculté de Médecine Université Paris Cité Descartes  
France

Anders Perner, MD, PhD  
Department of Intensive Care 4131  
Rigshospitalet, University of Copenhagen  
Denmark  
Lene Russell, MD, PhD  
Department of Intensive Care 4131  
Rigshospitalet, University of Copenhagen  
Denmark  
Kathryn Puxty, MD, PhD  
Department of Intensive Care  
Glasgow Royal Infirmary  
United Kingdoms  
Morten Hylander Møller, MD, PhD  
Department of Intensive Care 4131  
Rigshospitalet, University of Copenhagen  
Denmark  
Carl Thomas Anthon MD, PhD-student  
Department of Intensive Care 4131  
Rigshospitalet, University of Copenhagen,  
Denmark

**Management committee:**

Lene Russell, MD, PhD  
Department of Intensive Care 4131  
Rigshospitalet, University of Copenhagen  
Denmark  
Anders Perner, MD, PhD  
Department of Intensive Care 4131  
Rigshospitalet, University of Copenhagen  
Denmark  
Morten Hylander Møller, MD, PhD  
Department of Intensive Care 4131  
Rigshospitalet, University of Copenhagen  
Denmark  
Carl Thomas Anthon MD, PhD-student  
Department of Intensive Care 4131  
Rigshospitalet, University of Copenhagen,  
Denmark
Supplement 4 (S4): Outcomes and definitions.

Classification of thrombocytopenia
Patients with ‘thrombocytopenia at baseline’ will be defined as patients with at least one recorded platelet count below $150 \times 10^9$/L within 24 hours prior to ICU admission. Patients with ‘thrombocytopenia during ICU stay’ will be defined as patients with at least one recorded platelet count below $150 \times 10^9$/L during ICU stay without pre-existing thrombocytopenia at baseline. Patients with ‘any thrombocytopenia’ will be defined as patients with at least one recorded platelet count below $150 \times 10^9$/L at baseline and/or during ICU stay.

Primary outcome
The primary outcome is the number of patients with ‘any thrombocytopenia’ in the ICU, which is a composite outcome consisting of the number of patients with ‘thrombocytopenia at baseline’ and the number of patients with ‘thrombocytopenia during ICU stay’ as defined above.

Secondary outcomes
1. The number of patients with ‘any thrombocytopenia’, ‘thrombocytopenia at baseline’ and ‘thrombocytopenia during ICU stay’ categorised into the following subclasses according to the nadir platelet count:
   - Mild: $100 - 149 \times 10^9$/L.
   - Moderate: $50 - 99 \times 10^9$/L.
   - Severe: $20 - 49 \times 10^9$/L.
   - Very severe: $< 20 \times 10^9$/L.

2. Death within 90-days of ICU admission.

3. Days alive and out of hospital within 90 days of ICU admission. Days alive and out of hospital will be defined as the total number of days spent in hospital subtracted from the total study period of 90 days; i.e., if a patient is discharged 15 days after the index hospital admission and then readmitted to the hospital for a period of 10 days before second discharge, the total number of days alive and out of hospital is calculated as 90 – 15 – 10 days. Patients that die within the 90-day study period will be assigned zero days alive and out of hospital.
4. Days alive without the use of life-support defined as days alive without the use invasive mechanical ventilation, continuous infusion of vasopressors or inotropics, renal replacement therapy (including days between intermittent haemodialysis) and extracorporeal membrane oxygenation (ECMO). The total number of days alive without the use of life-support will be calculated as the total number of days with the use of life-support subtracted from the total study period of 90 days. Patients that die within the 90-day study period will be assigned zero days alive without the use if life-support.

5. Number of patients with at least one bleeding episode in the ICU graded into minor, mild, severe and debilitating bleeding events according the World Health Organization classification\(^1\) (available in supplement, S5). Each patient will only be counted once, and the highest graded bleeding episode will take priority. Bleeding occurring only during surgery will not be registered as a bleeding event.

6. Number of patients with at least one thrombotic event including peripheral arterial and venous thrombosis, acute coronary thrombosis, acute mesenterial ischemia, acute ischaemic stroke, central vein thrombosis, pulmonary embolus, and cerebral vein thrombosis (definitions available in supplement, S6). Each patient will only be counted once.

7. Number of patients that received at least one platelet transfusion during ICU stay, the number of units and volumes transfused and indications (prophylactic, pre-procedural, therapeutic).
   - **Pre-procedural** will be defined as any platelet transfusion administered in the ICU to prevent or reduce the risk of bleeding prior to an invasive procedure (e.g., central venous catheter placement, lumbar puncture, dialysis catheter placement, percutaneous dilatational tracheostomy, or surgery of any type).
   - **Prophylactic** will be defined as any non-procedural platelet transfusion administered in the ICU to prevent or reduce the risk of bleeding.
   - **Therapeutic** will be defined as any platelet transfusion administered in the ICU specifically due to bleeding.
Supplement 5 (S5): Modified World Health Organization classification.

The World Health Organization (WHO) bleeding scale\(^1\) has been used to grade bleeding episodes in a modified version in large multicentre trials assessing platelet transfusions in patients with haematological malignancy and hypo-proliferative thrombocytopenia.\(^2-5\) We used specific descriptors for each grade as previously used in these trials and adopted the scale to the intensive care unit setting (Table 5.1). To assist local investigators in the grading of bleeding episodes, we also listed the descriptors according to anatomical site (Table 5.1).

### Table 5.1 Modified World Health Organization\(^a\) bleeding scale

| Grade 1: Minor Blood Loss |
|---------------------------|
| – Petechiae (<2 mm in size). |
| – Purpura (< 2.5 cm diameter/1 inch). |
| – Subconjunctival bleeding. |
| – Upper airways: Oropharyngeal bleeding, epistaxis <30 minutes, not requiring packing\(^6\). |
| – Abnormal vaginal bleeding (non-menstrual; < 2 pads/day). |

| Grade 2: Mild Blood Loss (not requiring RBC transfusion) |
|--------------------------------------------------------|
| – Retinal bleeding without visual impairment. |
| – Profuse epistaxis or oropharyngeal bleeding >30 minutes or requiring packing\(^b\). |
| – Haemoptysis, blood in broncho-pulmonary lavage, blood in tracheal tube (intubated patients). |
| – Haematemesis, blood in nasogastric aspirates, melaena or haematochezia. |
| – Haematuria. |
| – Abnormal vaginal bleeding (>2 pads/day). |
| – Diffuse petechia/purpura, multiple haematomas or ecchymoses, each >2.5 cm or any one >10 cm. |
| – Musculoskeletal bleeding, soft tissue bleeding and bleeding in cavity fluids evident macroscopically. |
| – Abnormal bleeding from invasive or procedure sites. |

| Grade 3: Severe Blood Loss (requiring RBC transfusion)\(^c\) |
|----------------------------------------------------------|
| – CNS bleeding visible on imaging study but without neurological symptoms or clinical consequences\(^d\). |
| – Any bleeding requiring up to two RBC transfusions\(^e\) within 24 h of onset including epistaxis, oropharyngeal bleeding, haemoptysis, melaena, haematemesis, haematuria, haematochezia, |
vaginal bleeding, musculoskeletal bleeding, soft tissue bleeding and bleeding from invasive and procedure sites.

| Grade 4: Debilitating Blood Loss<sup>c</sup> |
|---------------------------------------------|
| – Debilitating or life-threatening bleeding; including any bleeding requiring either more than two units of RBC<sup>c</sup>, intubation and mechanical ventilation or a surgical intervention (including coiling) within 24 hours after onset. |
| – Non-fatal CNS bleeding resulting in neurological symptoms. |
| – Retinal bleeding with visual impairment. |
| – Fatal bleeding from any source. |

**Abbreviations:** Central nervous system (CNS), Red blood cells (RBC), Computed Tomography scan (CT).

<sup>a</sup>Specific descriptors for each grade of bleeding as previously described by Heddle et al. Blood 2009<sup>4</sup>

<sup>b</sup>Oropharyngeal bleedings > 30 minutes are classified as Grade 2 as in Stanworth et al. NEJM 2013<sup>2</sup>

<sup>c</sup>RBC transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding as in Slichter et al. NEJM 2010<sup>6</sup>

<sup>d</sup>CNS bleedings without neurological symptoms classified as Grade 3 as in Stanworth et al. NEJM 2013<sup>2</sup>
| Site                                      | Grade 1 (Minor)                          | Grade 2 (Mild)                          | Grade 3 (Severe)                                                       | Grade 4 (Debilitating)                                                                 |
|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| **Central Nervous System (CNS)**         | Retinal bleeding without visual impairment | - CNS bleeding visible on imaging study but without neurological symptoms or clinical consequence | - Any bleeding requiring up to two RBC transfusions over *routine transfusion needs* within 24 hours after onset of bleeding ** | - Retinal bleeding with visual impairment - Non-fatal CNS bleeding resulting in neurological symptoms or requiring an intervention - Any bleeding requiring one or more of the following within 24 hours after onset of bleeding: - more than 2 RBC over *routine transfusion needs* ** - intubation and mechanical ventilation - a surgical intervention including coiling |
| **Upper airways (oral and nasal cavities, pharynx)** | Oropharyngeal bleeding or epistaxis; total duration < 30 min | Oropharyngeal bleeding or epistaxis; total duration > 30 min or requiring packing | Any bleeding requiring up to two RBC transfusions over *routine transfusion needs* within 24 hours after onset of bleeding ** | Any bleeding requiring one or more of the following within 24 hours after onset of bleeding: - more than 2 RBC over *routine transfusion needs* ** - intubation and mechanical ventilation - a surgical intervention including coiling |
| **Lower airways / Intrathoracic cavity** | - Haemoptysis - Blood in broncho-pulmonary lavage - Blood in tracheal suction (intubated patients) - Bleeding from intra-thoracic organs or vascular structures not requiring RBC transfusion | Any bleeding requiring up to two RBC transfusions over *routine transfusion needs* within 24 hours after onset of bleeding ** | Any bleeding requiring one or more of the following within 24 hours after onset of bleeding: - more than 2 RBC over *routine transfusion needs* ** - intubation and mechanical ventilation |
| Gastrointestinal/Intraabdominal | Haematemesis - Coffee ground emesis - Blood in nasogastric aspirate - Melaena - Haematochezia - Bleeding from other abdominal or vascular structures | Any bleeding requiring up to two RBC transfusions over routine transfusion needs within 24 hours after onset of bleeding ** | Any bleeding requiring one or more of the following within 24 hours after onset of bleeding: - more than 2 RBC over routine transfusion needs** - intubation and mechanical ventilation - a surgical intervention including coiling |
|---|---|---|---|
| Genitourinary | Abnormal vaginal bleeding (non-menstrual; < 2 pads/day) - Haematuria - Abnormal vaginal bleeding (non-menstrual; ≥2 pads/day) | Any bleeding requiring up to two RBC transfusions over routine transfusion needs within 24 hours after onset of bleeding ** | Any bleeding requiring one or more of the following within 24 hours after onset of bleeding: - more than 2 RBC over routine transfusion needs** - intubation and mechanical ventilation - a surgical intervention including coiling |
| Skin, soft tissue, Musculoskeletal | Localised petechia (<2mm in size) - Purpura (<2.5 cm/1 inch diameter) - Subconjunctival bleeding - Diffuse petechia/purpura - Multiple spontaneous haematomas or ecchymoses > 2.5 cm or any one > 10 cm/4 inches - Musculoskeletal bleeding - Joint bleeding - Soft tissue bleeding | Any bleeding requiring up to two RBC transfusions over routine transfusion needs within 24 hours after onset of bleeding ** | Any bleeding requiring one or more of the following within 24 hours after onset of bleeding: - more than 2 RBC over routine transfusion needs** - intubation and mechanical ventilation - a surgical intervention including coiling |
### Invasive sites

- Abnormal bleeding from invasive sites (e.g. venipuncture sites, existing intravenous sites or catheter exit sites)

Any bleeding requiring up to two RBC transfusions over routine transfusion needs within 24 hours after onset of bleeding **

Any bleeding requiring one or more of the following within 24 hours after onset of bleeding:
- more than 2 RBC over routine transfusion needs**
- intubation and mechanical ventilation
- a surgical intervention including coiling

### Post-procedural sites

- Abnormal bleeding after procedures (e.g. central venous / dialysis catheters, biopsies, percutaneous dilatation tracheostomies, pleuracentesis)**
- Abnormal postoperative bleeding from surgical sites**

Any bleeding requiring up to two RBC transfusions over routine transfusion needs within 24 hours after onset of bleeding *

Any bleeding requiring one or more of the following within 24 hours after onset of bleeding:
- more than 2 RBC over routine transfusion needs*
- intubation and mechanical ventilation
- a surgical intervention including coiling

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Red Blood Cell (RBC) transfusion specifically related to treatment of bleeding within 24 hours of onset of bleeding.

** Bleeding specifically related to the invasive or surgical procedure.
Supplement 6 (S6): Definitions of thrombotic events.

Arterial thrombosis

Peripheral arterial thrombosis.
Defined as limb-threatening ischemia which is confirmed by limb haemodynamic or imaging and leads to an acute vascular intervention (i.e., pharmacologic, peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation) within 30 days of onset of symptoms. In the absence of confirmation by limb haemodynamic or imaging, absent pedal pulses is acceptable as hemodynamic criterion for acute limb ischemia.7

Acute coronary thrombosis.
Defined as ST-elevation myocardial infarction with imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology and/or identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.8

Acute mesenterial ischemia.
Defined as thrombus visible on CT scan or surgical findings/autopsy findings consistent with acute mesenterial ischemia.9

Acute ischemic stroke.
Defined as clinical symptoms in combination with relevant findings on a CT scan, or sign of thrombosis on computed tomography angiography (CTA) sites or MR imaging and magnetic resonance angiography (MRA).10

Venous thrombosis

Central vein thrombosis
Defined as a thrombosis visible on CT scan, venography or ultrasonography of central veins including the caval vein, and subclavian- and jugular veins11 as well as portal vein thrombosis12 and acute mesenteric venous thrombosis.13

Pulmonary embolus
Defined as thrombus visible on multidetector row computed tomography pulmonary angiogram (CTPA) in combination with clinical symptoms.14

Peripheral venous thrombosis
Defined as a thrombosis visible on CT scan or ultrasonography on peripheral veins. When ultrasound is used, any partial or incompressible venous segment in common femoral, proximal, middle and distal superficial femoral, and popliteal veins and the venous trifurcation is classified as a deep-vein thrombosis.15
Cerebral vein thrombosis
Defined as thrombus detected by magnetic resonance imaging (MRI) and MRI venography.¹⁰
Supplement 7 (S7): Baseline variables and definitions.

The variables below are registered at baseline which is equivalent to the time of the ICU admission.

Patient and admission characteristics.

- **Age (years).**
  Age at ICU admission.

- **Gender (male/female).**
  Genotypic gender of the patient.

- **Height.**
  Measured or estimated height in centimetres (cm) at ICU admission.

- **Weight.**
  Measured or estimated weight in kilograms (kg) at ICU admission.

- **ICU admission date.**

- **Hospital admission date.**
  The date of admission to the first hospital, where the patients was admitted, during the current hospitalization.

- **Source of ICU admission.**
  - Emergency department (Any accident/emergency/casualty/acute department or directly from the pre-hospital setting by an ambulance service or similar).
  - General ward.
  - Operating or recovery room (including any surgical theatre, endoscopy and angiography suite, any recovery facilities observing post-operative patients).
  - Another ICU.

- **Elective surgery, (y/n).**
  Surgery planned 24 hours or mere in advance during the current hospitalization but prior to ICU admission.

- **Emergency surgery, (y/n).**
Surgery planned less than 24 hours in advance during the current hospitalisation but prior to ICU admission.

- **Main reason for ICU admission.**
  - Neurological condition.
  - Respiratory failure.
  - Circulatory failure.
  - Renal failure.
  - Liver failure.
  - Metabolic condition.
  - Multiple trauma.
  - Burn injury.
  - Severe haemorrhage.
  - Other.

**Comorbidities prior to ICU admission.**

- **Chronic pulmonary disease, (y/n).**
  Treatment at time of hospital admission with any relevant drug indicating chronic pulmonary disease (e.g. COPD, asthma). e.g. albuterol, levalbuterol, salmeterol, formoterol, arformoterol, indacaterol, vilanterol, olodaterol, tiotropium, aclidinium, umeclidinium, glycopyrronium, budesonide and fluticasone.

- **Ischaemic heart disease or heart failure, (y/n).**
  Previous myocardial infarction, invasive intervention for coronary artery disease, stable or unstable angina, NYHA class 3 or 4 or measured LVEF < 40%.

- **Chronic renal failure, (y/n).**
  Need for chronic renal support including continuous or intermittent renal replacement therapy or S-creatinine > 3.6 g/dL / 300 µmol/L prior to hospital admission.

- **Chronic liver failure, (y/n).**
  Including any of the following: portal hypertension, cirrhosis (proven by biopsy, computed tomography (CT) scan or ultrasound), history of variceal bleeding or hepatic encephalopathy.

- **Solid tumour cancer, (y/n).**
  Presence of a solid non-haematological malignant tumour confirmed by surgery, CT scan or any other method.
- **If yes: Metastatic cancer, (y/n).**
  Proven non-haematological metastasis by surgery, CT-scan, or any other method.

- **Haematological malignancy, (y/n).**
  Including any of the following: acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), chronic lymphocytic leukaemia (CLL), chronic myelogenous leukaemia (CML), t-cell prolymphocytic leukaemia (T-PLL), b-cell prolymphocytic leukaemia (B-PLL), large granular lymphocytic leukaemia (LGL), lymphomas including Hodgkin’s lymphoma and non-Hodgkin lymphoma (e.g., small lymphocytic lymphoma (SLL), lymphoblastic lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hairy cell leukaemia (HCL), Marginal zone lymphoma (MZL), Burkitt’s lymphoma (BL), Post-transplant lymphoproliferative disorder (PTLD), Waldenstöm’s macroglobulinemia, NK- or T-cell lymphomas), multiple myeloma/plasma cell myeloma, myelodysplastic syndrome, other myeloproliferative neoplasms (MPN) including chronic neutrophilic leukaemia, primary myelofibrosis (PMF) and mast cell disease.

  - **If yes: Type of haematological malignancy.**
    - Acute lymphoblastic leukaemia (ALL)
    - Acute myelogenous leukaemia (AML)
    - Chronic myelogenous leukaemia (CML)
    - Chronic lymphocytic leukaemia (CLL)
    - Large granular lymphocytic leukaemia (LGL)
    - Hodgkin’s lymphoma
    - Non-Hodgkin lymphoma
    - T-cell prolymphocytic leukaemia (T-PLL)
    - B-cell prolymphocytic leukaemia (B-PLL)
    - Multiple myeloma/plasma cell myeloma
    - Myelodysplastic syndrome
    - Other myeloproliferative neoplasms

- **Non-malignant haematological emergency, (y/n).**
  Including any of the following: thrombotic thrombocytopenic purpura (TTP), atypical haemolytic uraemic syndrome (aHUS), shiga toxin-producing Escherichia coli HUS (STEC-HUS), autoimmune haemolytic anaemia (AIHA) including primary and secondary AIHA and drug induced AIHA, hemophagocytic lymphohistiocytosis, acute antiphospholipid syndrome.

  - **If yes: Type of non-malignant haematological emergency.**
    - Thrombotic thrombocytopenic purpura (TTP)
    - Atypical haemolytic uraemic syndrome (aHUS)
    - Shiga toxin-producing Escherichia coli HUS (STEC-HUS)
- Autoimmune haemolytic anaemia (AIHA)
- Haemophagocytic lymphohistiocytosis
- Acute antiphospholipid syndrome

- **Chronic spleen enlargement, (y/n).**
  Craniocaudal length >13 cm diagnosed by computed tomography (CT), ultrasonography or magnetic resonance imaging (MRI).

- **Immune deficiencies, (y/n).**
  Non-AIDS-related immune deficiencies (including solid organ transplant) requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.
    - If yes: Solid organ transplant, (y/n).

- **Hereditary or acquired coagulation disorders, (y/n).**
  Includes any of the following: haemophilia A or B, Von Willebrand's disease, inherited deficiencies of factors I (fibrinogen), II (prothrombin), V, VII, X, XI, and XIII, Glanzmann's thrombasthenia, Bernard-Soulier syndrome, gray platelet syndrome (platelet alpha-granule deficiency), May-Hegglin anomaly, factor V Leiden, prothrombin gene mutation, inherited deficiencies of protein C, S or antithrombin, inherited increased levels of homocysteine, or fibrinogen or dysfibrinogenemia, antiphospholipid antibody syndrome, essential thrombocytosis.

- **History of venous thrombo-embolism (y/n).**
  Includes any venous or arterial thrombo-embolisms including those defined in supplement, S5.

**Treatments prior to ICU admission.**

- **Haematopoietic stem cell transplantation, (y/n).**
  Includes both autologous and allogeneic stem cell transplantations within 1 year prior to ICU admission.

- **Treatment with chemotherapy, (y/n).**
  Treatment with chemotherapy within 6 weeks prior to ICU admission. Includes treatment with any of the following: Bortezomib, Carboplatin, Cisplatin, Cyclophosphamide, Dacarbazine, Docetaxel, Doxorubicin, Etoposide, Fluorouracil, Gemcitabine, Hydroxycarbamide, Ibritumomab tiuxetan, Ifosfamide, Irinotecan, Leucovorin, Methotrexate, Oxaliplatin, Panobinostat, Temozolomide, Tamoxifen, Vincristine.
• **Treatment with drugs that may affect platelet count, (y/n).**
  Treatment with any of the following drugs within 1 week prior to ICU admission: Piperacillin, Rituximab, Abciximab, Carbamazepine, Valproic acid, Interferon-alfa.

• **Treatment with anticoagulating agents, (y/n).**
  Includes treatment with unfractionated heparin, low-molecular weight heparin (LMWH), new oral anticoagulant drugs (NOAC), vitamin K-antagonists and intravenous direct thrombin inhibitors in any dose within 48 hours of ICU admission.
  - If yes: **Specify the anticoagulant agent.**
    - Unfractionated heparin (UFH).
    - Low-molecular weight heparin (LMWH).
    - Other (including NOAC, vitamin K-antagonists and direct thrombin inhibitors).
  - If yes: **Specify the dose of the anticoagulating agent (as determined by the treating clinician).**
    - Prophylactic dose.
    - Therapeutic dose.

• **Treatment with platelet inhibitors, (y/n).**
  Includes treatment with ADP-receptor inhibitors, acetylsalicylic acid, dipyridamole within 48 hours of ICU admission.
  - If yes: **Specify the platelet inhibitor.**
    - ADP-receptor inhibitors.
    - Acetylsalicylic acid.
    - Dipyridamole.

**Acute conditions**

• **Acute liver failure at ICU admission, (y/n).**
  Severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy within eight weeks of the first symptoms (i.e., jaundice) in the absence of pre-existing liver disease.17,18

• **Sepsis or septic shock at ICU admission according to the Sepsis 3 consensus definition19 within the first 24 hours of ICU admission.**
  - Sepsis, (y/n).
    A suspected or confirmed site of infection or positive blood culture AND an acute change in total SOFA score ≥ 2 points consequent to the infection
  - Septic shock, (y/n).
A suspected or confirmed site of infection or positive blood culture AND ongoing infusion of vasopressor/inotrope agent to maintain a mean arterial blood pressure of 65 mmHg or above AND Lactate of 2 mmol/L or above in any plasma sample.

- **Positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) / Coronavirus disease 2019 (COVID-19), (y/n).**
  Any sample from airway secretions or nasopharyngeal swab positive for SARS-CoV-2/COVID-19 at any time leading to or during current hospital admission prior to ICU admission.

**Laboratory values**

- **Habitual platelet count.**
  Highest platelet count within 6 months prior to current hospitalisation. If no value is available, the highest platelet count within 12 months prior to hospitalisations may be used. If no platelet count within 12 months prior to hospitalisation is available, the habitual platelet count is estimated. Unit: cells x 10^9/L.

- **Platelet count.**
  Latest platelet count within 24 hours prior to ICU admission. Unit: cells x 10^9/L.

- **Haemoglobin.**
  Latest haemoglobin within 24 hours prior to ICU admission. Unit: mmol/L or g/L.

- **White blood cell count.**
  Latest white blood cell count within 24 hours prior to ICU admission. Unit: cells x 10^9/L.

- **White blood cell differential count.**
  Latest white blood cell differential count within 24 hours prior to ICU admission. Unit: cells x 10^9/L
  - Neutrophils.
  - Lymphocytes.
  - Monocytes.
  - Eosinophils.
  - Basophils.

- **International normalised ratio (INR).**
  Latest INR within 24 prior to ICU admission.
• **Lactate dehydrogenase (LDH).**
  Latest LDH within 24 prior to ICU admission. Unit: U/L.

• **Fibrinogen.**
  Latest fibrinogen within 24 prior to ICU admission. Unit: µmol/L or g/L.

• **Presence of schistocytes, (y/n).**
  Peripheral blood smear positive for schistocytes within 24 hours prior to ICU admission.

**Bleeding**

• **Bleeding event according to the WHO classification, (y/n).**
  Any bleeding event according to the WHO classification within 24 hours prior to ICU admission. Bleeding occurring only during surgery will not be registered as a bleeding event.
  
  o  **If yes:** Specify site of bleeding.
  
  ▪ Upper airways.
  ▪ Skin, soft tissue or musculoskeletal.
  ▪ Intra-abdominal / gastrointestinal.
  ▪ Genitourinary.
  ▪ Intra-thoracic / Lower airways.
  ▪ Central nervous system (CNS)
  ▪ Invasive sites
  ▪ Post-procedural.

**Platelet transfusions**

• **Platelet transfusion, (y/n).**
  Any platelet transfusion administered within 24 hours prior to ICU admission.
  
  o  **If yes:**
  
  ▪ Total volume (mL) of pooled buffy coat (random donor) platelets.
  
  ▪ Total units of pooled buffy coat (random donor) platelets.
  
  ▪ Total volume (mL) of apheresis platelets (single donor platelets).
  
  ▪ Total units of apheresis platelets (single donor platelets).
Simplified Mortality Score for the Intensive Care unit (SMS-ICU).
Variables for the SMS-ICU\textsuperscript{20,21} not included in the variables above or in the variables registered daily.

- Lowest measured systolic blood pressure (mmHg).
  Lowest systolic blood pressure (invasive or non-invasive) in the first 24 hours after ICU admission.
Supplement 8 (S8): Daily registered variables and definitions.
The variables below are registered daily during the ICU admission until the end of the 90-day follow-up period, discharge from the ICU or death. If an enrolled patient is transferred directly between participating ICUs or readmitted (with an intermittent stay in e.g. a general ward or at home) to a participating ICU within the 90-day follow-up period, the daily data collection will be continued. The timespan of the dayform corresponds to calendar days, i.e., 00:00 – 23:59. The timespan of the dayform will be shorter on days of admission, discharge or death.

Life support

- **Infusion of vasopressors, (y/n).** Any continuous treatment with norepinephrine, epinephrine, phenylephrine, vasopressin analogues, dopamine, dobutamine, milrinone or levosimendan.

- **Invasive mechanical ventilation, (y/n).** Invasive mechanical ventilation is defined as the use of positive pressure ventilation using a ventilator via a cuffed tube (oral, nasal or tracheostomy). CPAP is NOT invasive mechanical ventilation.

- **Renal replacement therapy, (y/n).** Any form of renal replacement therapy (e.g. dialysis, hemofiltration or hemodiafiltration) at any rate. Including days between intermittent renal replacement therapy.

- **Extracorporeal membrane oxygenation (ECMO), (y/n).** Any form of extracorporeal membrane oxygenation.

- **Therapeutic plasma exchange therapy (TPE), (y/n).** Any form of therapeutic plasma exchange therapy.

Treatments

- **Treatment with drugs that may affect platelet count, (y/n).** Treatment with any of the following drugs: Piperacillin, Rituximab, Abciximab, Carbamazepine, Valproic acid, Interferon-alfa.

- **Treatment with anticoagulating agents, (y/n).** Includes treatment with unfractionated heparin, low-molecular weight heparin (LMWH),
new oral anticoagulant drugs (NOAC), vitamin K-antagonists and intravenous direct thrombin inhibitors in any dose.

- If yes: Specify the anticoagulant agent.
  - Unfractionated heparin (UFH).
  - Low-molecular weight heparin (LMWH).
  - Other (including NOAC, vitamin K-antagonists and direct thrombin inhibitors).

- If yes: Specify the dose of the anticoagulating agent (as determined by the treating clinician).
  - Prophylactic dose.
  - Therapeutic dose.

- Treatment with platelet inhibitors, (y/n).
  Treatment with ADP-receptor inhibitors, acetylsalicylic acid, dipyridamole.

  - If yes: Specify the platelet inhibitor.
    - ADP-receptor inhibitors.
    - Acetylsalicylic acid.
    - Dipyridamole.

**Laboratory values**

If any of the laboratory results are unobtainable within the timespan of the first ICU day (from ICU admission until 23:59), available values from the same calendar day may be used. For the remaining days (second ICU day an onwards), laboratory results obtained +/- 3 hours outside the timespan of the dayform may be used unless that it has already been used in another dayform.

- **Lowest platelet count.**
  Unit: cells x 10⁹/L.

- **Lowest haemoglobin.**
  Unit: mmol/L or g/L.

- **White blood cell count.**
  If multiple values, the highest value will be registered. Unit: cells x 10⁹/L.

- **White blood cell differential count.**
  If multiple values, the highest value will be registered. Unit: cells x 10⁹/L.
  - Neutrophils.
- Lymphocytes.
- Monocytes.
- Eosinophils.
- Basophils.

- **International normalised ratio (INR).**
  If multiple values, the highest value will be registered.

- **Lactate dehydrogenase (LDH).**
  If multiple values, the highest value will be registered. Unit: U/L.

- **Fibrinogen.**
  If multiple values, the highest value will be registered. Unit: µmol/L or g/L.

- **Presence of schistocytes, (y/n).**
  Peripheral blood smear positive for schistocytes.

- **Lowest arterial partial pressure of oxygen (P_aO_2).**
  If the patient received mechanical ventilation on this day, the lowest P_aO_2 during mechanical ventilation will be registered. If a value for P_aO_2 is not available (i.e., no arterial gas sampled), the P_aO_2 will be estimated from the lowest peripheral oxygen saturation (S_pO_2) using the conversions table provided in supplement, S9.

- **Corresponding fraction of inspired oxygen (FiO_2).**
  The fraction of inspired oxygen at the time of the lowest P_aO_2. For closed systems, the set FiO_2 on the ventilator will be registered. For open systems, the FiO_2 will be estimated according to supplement, S10.

**Surgery and transfusions in the operating room.**

- **Surgery, (y/n).**
  Any surgery performed in the operating room.
  - If yes: **Transfusion with platelets during surgery, (y/n).**
    Any type of platelet transfusion in the operating room.
    - If yes:
      - Total units of platelets transfused.

    - Total volume (mL) of platelets transfused.
If yes: Transfusion with red blood cells (RBCs) during surgery, (y/n). Any type of RBC transfusion in the operating room.
  - If yes:
    • Total number of units of RBCs transfused.
    • Total volume (mL) of RBC transfused.

If yes: Transfusion with plasma during surgery, (y/n). Any type plasma transfusion in the operating room.
  - If yes:
    • Total number of units of plasma transfused.
    • Total volume (mL) of plasma transfused.

Transfusions in the ICU

• Transfusion with platelets (y/n). Any type of platelet transfusion in the operating room.
  - If yes:
    ▪ Platelet count prior to transfusion.
      The latest platelet count prior to transfusion(s). If there are multiple transfusion episodes on the same day, we will register the highest platelet count prior to any of the episodes.
    ▪ Total volume (mL) of pooled buffy coat (random donor) platelets.
    ▪ Total units of pooled buffy coat (random donor) platelets.
    ▪ Total volume (mL) of apheresis platelets (single donor platelets).
    ▪ Total units of apheresis platelets (single donor platelets).

• Indications for platelet transfusion.
  • Pre-procedural (any platelet transfusion administered in the ICU to prevent or reduce the risk of bleeding prior to an invasive procedure (e.g. central venous catheter placement, lumbar puncture, dialysis
catheter placement, percutaneous dilatational tracheostomy or surgery of any type).

- Prophylactic (any non-procedural platelet transfusion administered in the ICU to patients to prevent or reduce the risk of bleeding)
- Therapeutic (any platelet transfusion administered in the ICU specifically due to bleeding).

- Transfusion with RBCs (y/n).
  - If yes:
    - Total volume (mL) of RBC transfused.
    - Total units of RBC transfused.

- Transfusion with plasma (y/n).
  Any type of plasma product transfused including fresh frozen plasma, cryoprecipitate, cryodepleted plasma and octaplasLG.
  - If yes:
    - Total volume (mL) of plasma transfused.
    - Total units of plasma transfused.

**Bleeding in the ICU**

- **Bleeding event according to the WHO classification, (y/n).**
  Any bleeding event according to the WHO classification in the ICU. Bleeding occurring only during surgery will not be registered as a bleeding event. The WHO classification is provided in supplement, S5.
  - If yes:
    - Bleeding grade according to the WHO classification.
      - Grade 1 – Minor blood loss.
      - Grade 2 – Mild blood loss.
      - Grade 3 – Severe blood loss.
      - Grade 4 – Debilitating blood loss.

    - Site of highest graded bleeding event according to the WHO classification.
      - Upper airways.
      - Skin, soft tissue or musculoskeletal.
• Intra-abdominal / gastrointestinal.
• Genitourinary.
• Intra-thoracic / Lower airways.
• Central nervous system (CNS)
• Invasive sites
• Post-procedural.

- **Bleeding from multiple sites according to the WHO classification (y/n).**
  - If yes:
    - **Additional sites.**
      - Upper airways.
      - Skin, soft tissue or musculoskeletal.
      - Intra-abdominal / gastrointestinal.
      - Genitourinary.
      - Intra-thoracic / Lower airways.
      - Central nervous system (CNS)
      - Invasive sites
      - Post-procedural.

**Thrombosis**

- **New thrombotic event, (y/n).**
  Any new (not previously registered) venous or arterial thrombosis including those defined in the supplement, S6.
  - If yes:
    - **Type of thrombotic event.**
      - Peripheral arterial thrombosis.
      - Acute coronary thrombosis.
      - Acute mesenterial ischemia.
      - Acute ischemic stroke.
      - Central vein thrombosis.
      - Pulmonary embolus.
      - Peripheral venous thrombosis.
      - Cerebral vein thrombosis.

- **Requirement for an intervention for the thrombotic event, (y/n).**
**Supplement 9 (S9): Estimation of partial pressure of oxygen (PaO₂)**

If PaO₂ is not available (i.e., no arterial blood gas was analysed), the lowest PaO₂ will be estimated from the lowest S₉O₂ according to the following conversion table:

| S₉O₂ | P₉O₂ (mmHg) | P₉O₂ (kPa) |
|------|-------------|------------|
| 80   | 44          | 5.9        |
| 81   | 45          | 6.0        |
| 82   | 46          | 6.1        |
| 83   | 47          | 6.3        |
| 84   | 49          | 6.5        |
| 85   | 50          | 6.7        |
| 86   | 52          | 6.9        |
| 87   | 53          | 7.1        |
| 88   | 55          | 7.3        |
| 89   | 57          | 7.6        |
| 90   | 60          | 8.0        |
| 91   | 62          | 8.3        |
| 92   | 65          | 8.7        |
| 93   | 69          | 9.2        |
| 94   | 73          | 9.7        |
| 95   | 79          | 10.5       |
| 96   | 86          | 11.5       |
| 97   | 96          | 12.8       |
| 98   | 112         | 14.9       |
| 99   | 145         | 19.3       |
Supplement 10 (S10): Estimation of the fraction of inspired oxygen (FiO₂)

Closed systems:
If the patient receives respiratory support on a closed system, the set FiO₂ on the ventilator will be registered.

Open systems:
If the patient receives respiratory support on an open system, the FiO₂ will be estimated according to the tables below.

Table 9.1. Nasal cannula

| Flow of oxygen (L/min) | FiO₂ |
|------------------------|------|
| 0                      | 0.21 |
| 1                      | 0.24 |
| 2                      | 0.28 |
| 3                      | 0.32 |
| 4                      | 0.36 |
| 5                      | 0.40 |
| 6                      | 0.44 |
| 7                      | 0.48 |
| 8                      | 0.52 |
| 9                      | 0.56 |
| 10                     | 0.60 |

Table 9.2. Hudson mask or similar

| Flow of oxygen (L/min) | FiO₂ |
|------------------------|------|
| 6                      | 0.45 |
| 8                      | 0.50 |
| 10                     | 0.54 |
| 15                     | 0.59 |
| 30                     | 0.65 |

Table 9.3. Hudson mask or similar when using air/oxygen mixtures

| Flow of oxygen/ air (L/min) | FiO₂ |
|-----------------------------|------|
| 3L O₂ / 12L air             | 0.29 |
| 7.5 L O₂ / 7.5L air         | 0.41 |
Venturi mask: the FiO₂ as indicated by the colour code will be used (0.24 – 0.60)

Reservoir-mask: (non-rebreather masks) with oxygen flows > 10 L/min: a FiO₂ of 0.95 will be used.

High-flow Nasal Oxygen (HFNO) therapy:

Several factors influence the achieved FiO₂ when using HFNO. The table below can be used when estimating the actual delivered FiO₂ when using High-flow nasal cannula systems (oxygen supply system delivering up to 100% humidified and heated oxygen at high flow rates).

### Table 9.4. High-flow Nasal Oxygen therapy

| Flow (L/min) | Delivered fraction of prescribed FiO₂ | FiO₂ 100% | FiO₂ 80% | FiO₂ 60% | FiO₂ 50% | FiO₂ 40% | FiO₂ 30% |
|--------------|--------------------------------------|-----------|----------|----------|----------|----------|----------|
| 10           | 0.60                                 | 0.60      | 0.48     | 0.36     | 0.30     | 0.24     | 0.18     |
| 15           | 0.70                                 | 0.70      | 0.56     | 0.42     | 0.35     | 0.28     | 0.21     |
| 20           | 0.75                                 | 0.80      | 0.60     | 0.45     | 0.38     | 0.30     | 0.23     |
| 25           | 0.80                                 | 0.80      | 0.64     | 0.48     | 0.40     | 0.32     | 0.24     |
| 30           | 0.85                                 | 0.90      | 0.68     | 0.51     | 0.43     | 0.34     | 0.26     |
| 35           | 0.87                                 | 0.90      | 0.70     | 0.52     | 0.44     | 0.35     | 0.26     |
| 40           | 0.90                                 | 0.90      | 0.72     | 0.54     | 0.45     | 0.36     | 0.27     |
| 45           | 0.95                                 | 1.00      | 0.76     | 0.57     | 0.48     | 0.38     | 0.29     |
| 50           | 1.00                                 | 1.00      | 0.80     | 0.60     | 0.50     | 0.40     | 0.30     |
| 55           | 1.00                                 | 1.00      | 0.80     | 0.60     | 0.50     | 0.40     | 0.30     |
| 60           | 1.00                                 | 1.00      | 0.80     | 0.60     | 0.50     | 0.40     | 0.30     |
Supplement 11 (S11): Discharge and readmission variables and definitions.

- **Discharge from the ICU, (y/n).**
  Patients who have been discharged from a participating ICU.

- **Date and time of ICU discharge.**

- **Patient discharged to:**
  - General ward.
  - ICU participating in the PLOT-ICU study.
  - ICU not participating in the PLOT-ICU study.
  - Home or unit outside the hospital.
  - Dead.

- **Readmission to the ICU, (y/n).**
  Patients who have been discharged from a participating ICU and readmitted to a participating ICU during the 90-day follow-up period.

- **Date and time of ICU readmission.**
Supplement 12 (S12): 90-day follow-up variables and definitions.

- **Did the patient die within 90 days after inclusion in the PLOT-ICU study, (y/n).**
  Definition: Death from any cause within the 90-day follow-up period including outpatient follow-up in the case of hospital discharge.

- **Date of death**

- **Was the patient discharged from the hospital alive within 90 days after inclusion in the PLOT-ICU study, (y/n).**
  Definition: Discharge alive from the index hospital admission (where the patient were included in the PLOT-ICU study) at any time during the 90-day follow-up period even if the patient was later readmitted.

- **Date of index hospital discharge.**

- **Additional hospital admissions within 90 days after inclusion in the PLOT-ICU study, (y/n).**
  Definition: Patients who has been discharged from the index hospital admission and readmitted to the hospital within the 90-day follow-up period.

- **Dates of additional hospital readmissions and discharges.**
Supplement 13 (S13): Information on participating ICUs.

- **Type of hospital.**
  - University hospital.
  - Non-university hospital.

- **Type of ICU.**
  - Medical ICU.
  - Surgical ICU.
  - Mixed ICU.

- **Number of beds open for admission.**
  - < 10.
  - 10-19.
  - 20-29.
  - ≥30.

- **Presence of a general guideline / protocol for platelet transfusions in the hospital (y/n).**

- **Presence of a specific guideline / protocol for platelet transfusions in the ICU, (y/n).**
Supplement 14 (S14): Simplified Mortality Score for the Intensive Care Unit (SMS-ICU).

| Variable                                      | Points |
|----------------------------------------------|--------|
| **Age (years)**                              |        |
| ≤ 39                                         | 0      |
| 40 – 59                                      | 5      |
| 60 – 79                                      | 10     |
| ≥ 80                                         | 13     |
| **Lowest systolic blood pressure (mmHg)**     |        |
| ≤ 49                                         | 6      |
| 50 – 69                                      | 5      |
| 70 – 89                                      | 3      |
| ≥ 90                                         | 0      |
| **Acute surgical admission**                 |        |
| No                                           | 3      |
| Yes                                          | 0      |
| **Haematological malignancy or metastatic cancer** |      |
| No                                           | 0      |
| Yes                                          | 7      |
| **Vasopressors / inotropes**                 |        |
| No                                           | 0      |
| Yes                                          | 4      |
| **Respiratory support**                      |        |
| No                                           | 0      |
| Yes                                          | 5      |
| **Renal replacement therapy**                |        |
| No                                           | 0      |
| Yes                                          | 4      |
| **Total score**                              | 0-42   |

*Continuous use of any vasopressor or inotrope.

*aUse of respiratory support, including invasive or non-invasive respiratory support and continuous use of continuous positive airway pressure (CPAP). Intermittent use of CPAP is not considered respiratory support.

*bUse of renal replacement therapy includes any renal replacement therapy whether chronic or acute, including continuous renal replacement therapy and intermittent hemodialysis, including the days in between intermittent hemodialysis.

*dPoints assigned for the different variables in the score. It is not possible to obtain a total score of 1, 2 or 40 points. The worst value recorded during the first 24 h in the ICU is used.
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