Standard Operating Procedure

Welcome participating in the InPUT-study! With this Standard Operating Procedure, we hope to be able to help you work with REDCAP, and to guide you in filling in the questions in this online case report form.

Please, if you encounter any difficulties, or if you have questions, do not hesitate to contact the InPUT steering team via inputstudy@amsterdamumc.nl

We are glad to help you, since we're pleased you're participating!

Kind regards,

The InPUT steering committee

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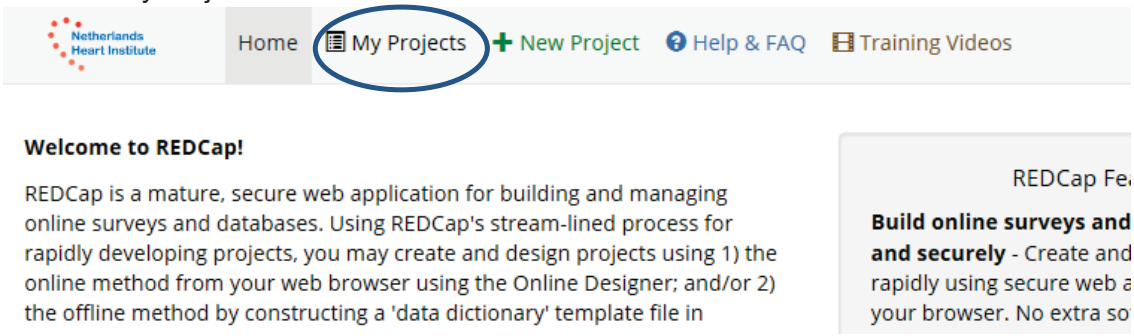
REDCap

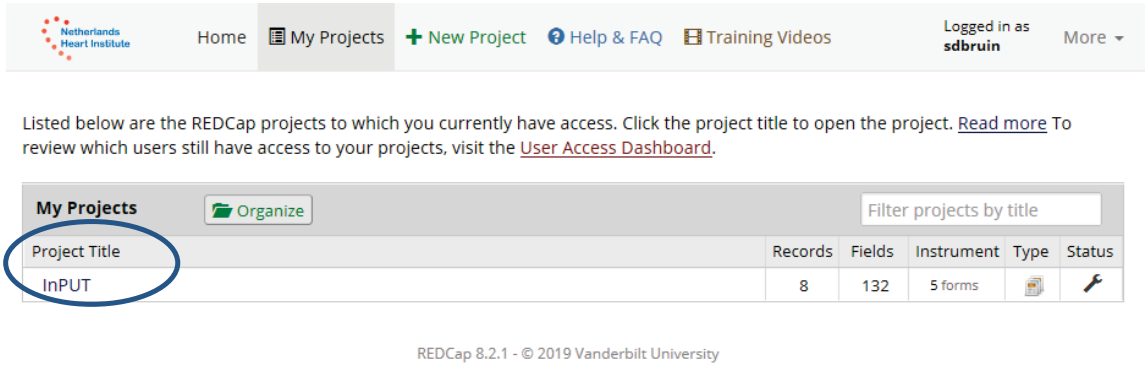
1. Send your name and email address to your national coordinator. He/she will collect the email addresses of the participating centers, and send this conglomerate to one of the coordinating researchers in the AMC, Amsterdam.

2. You will receive an email from REDCap with a link to set your password and an email that access was granted to the project **InPUT**.
   Set your password and login to REDCap.

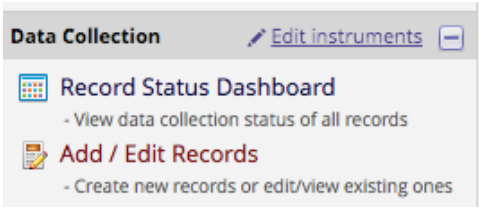
3. Click on “My Projects”



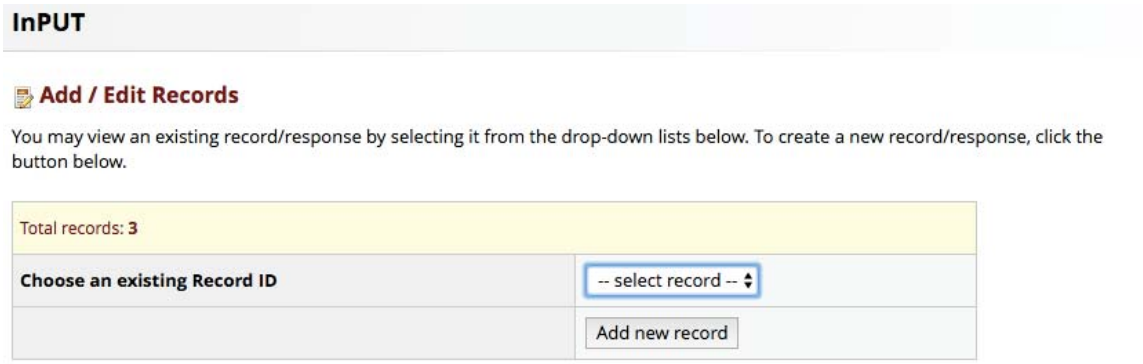
4. Click on “InPUT”



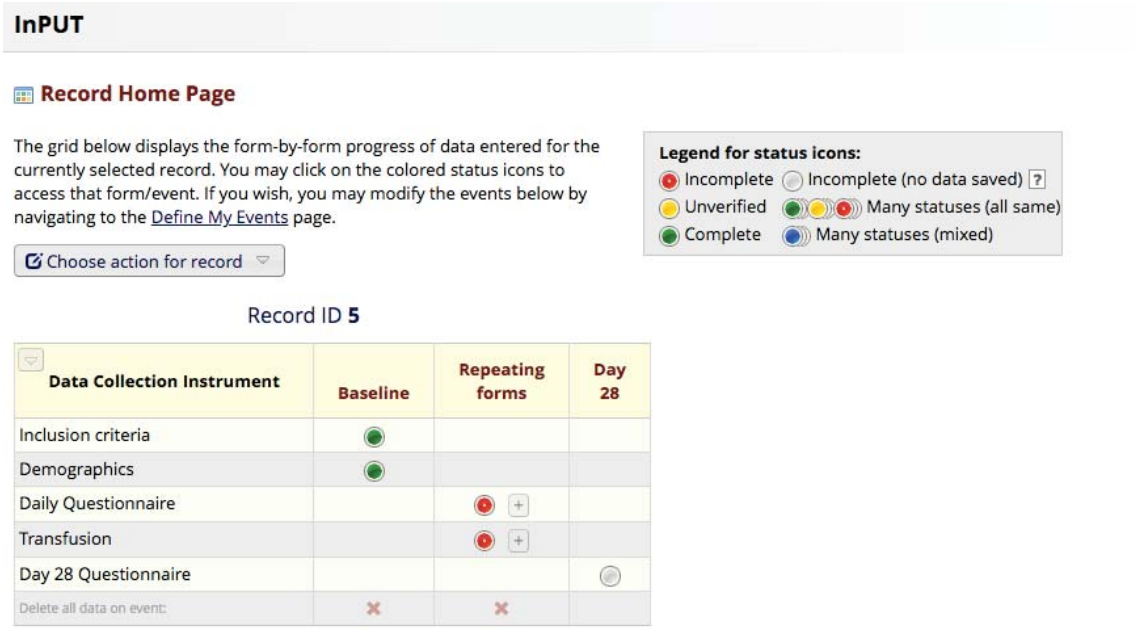
5. Click on “View/edit records”



6. Here you have two options:
   1) You can create a new record by clicking on “Add new record”, hereby creating a new record for a new patient you have not filled in any data for yet; or
   2) Reopen a record you have been working on before by clicking on “select record”



7. Now you can find yourself on the main page of this patient record.

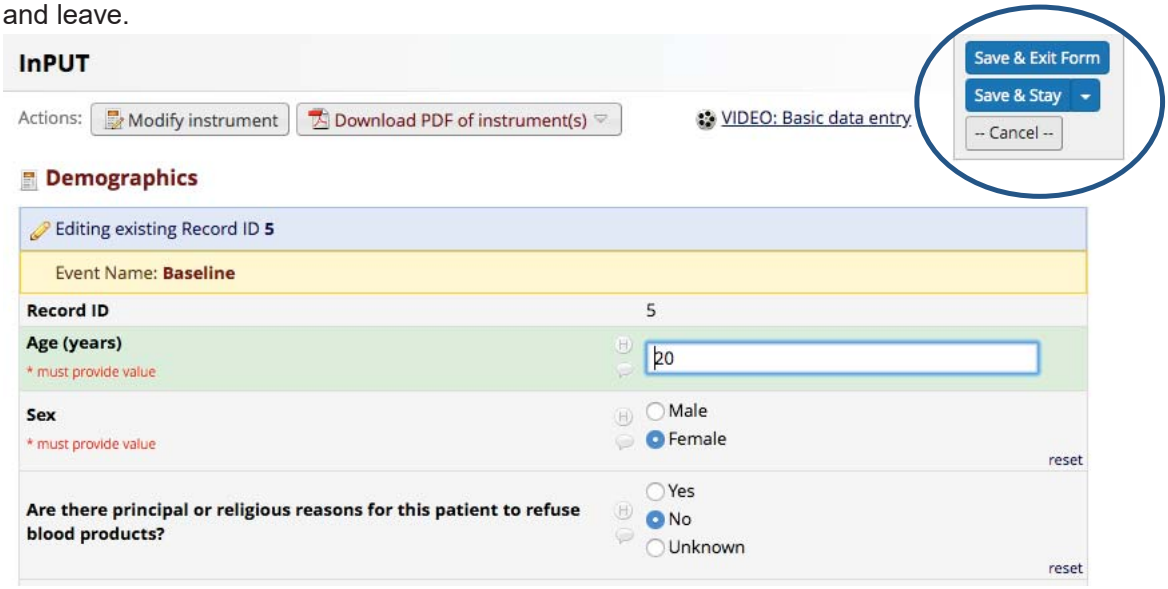


Here, you can see different dots referring to different current statuses of the parts of the patient record:
grey = incomplete, no data saved
red = incomplete, some data saved
yellow = unverified
green = complete
The baseline record of the patient record consists of the ‘chapter’ inclusion criteria and demographics. During the ICU admission of the patient, you fill in the daily questionnaire every day. Also, in case of transfusion of a blood product, you fill in the transfusion tab. You can add another day or transfusion event by clicking on the ‘plus’ sign. Finally, at day 28, you also fill in the questions regarding outcome in the chapter ‘Day 28 questionnaire’.

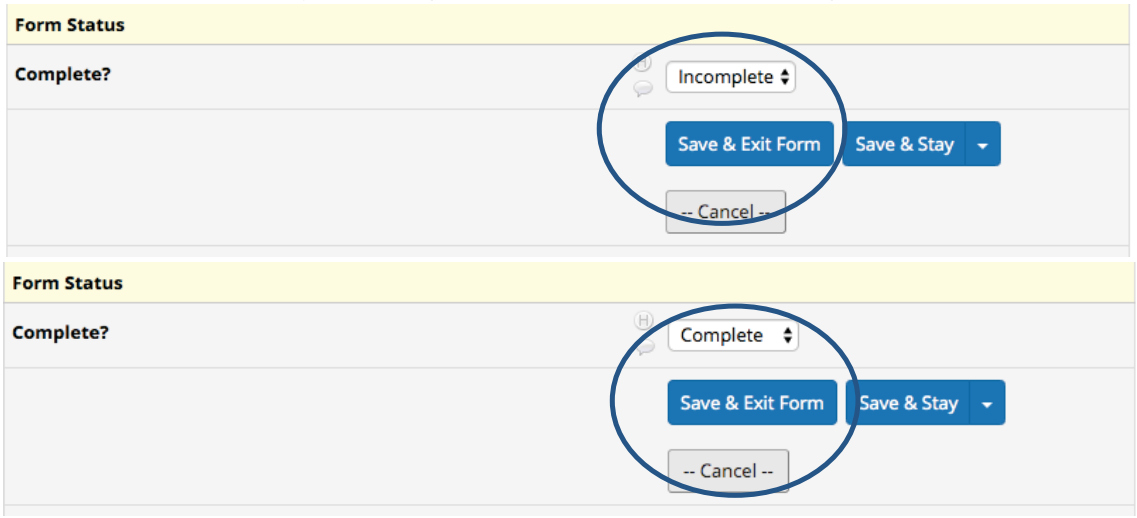
8. Fill in the questionnaire. You don't have to fill in all questions at once. You can always 'Save & Exit' the form and come back later.

   There are several options available to save your form.

   1. Click on 'Save & Exit form' in the upper right corner in case you want to save the form and leave.



   2. Click on 'Save & Exit form' all the way at the end of the form. Here, you can also see the current status of your form (complete, incomplete, unverified).



LIST OF ABBREVIATIONS & DEFINITIONS

ABBREVIATIONS

ACS	acute coronary syndrome
AKI	acute kidney injury
aPTT	activated partial thromboplastin time
APACHE IV	ability of the acute physiology and chronic health evaluation IV
ARDS	acute respiratory distress syndrome
BIVAD	biventricular assisting device
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
DOAC	direct oral anticoagulant
DIC	Disseminated intravascular coagulation
EuroSCORE	European system for cardiac operative risk evaluation
Hb	hemoglobin
hCVA	Hemorrhagic cerebrovascular accident
Ht	hematocrit
HIT	heparin induced thrombocytopenia
IABP	intra-aortic balloon pump
iCVA	Ischemic cerebrovascular accident
ICU	intensive care unit
INR	international normalized ratio
ITP	idiopathic thrombocytopenic purpura
LVAD	left ventricular assisting device
MAP	mean arterial pressure
PT	prothrombin time
RVAD	right ventricular assisting device
SOFA	sequential organ failure assessment score
TTP	thrombotic thrombocytopenic purpura
VA-ECMO	veno-arterial extracorporeal membrane oxygenation
VV-ECMO	veno-venous extracorporeal membrane oxygenation

DEFINITIONS

Acute coronary syndrome (ACS)
A group of clinical symptoms compatible with acute myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina to non-ST-segment elevation myocardial infarction to ST-segment elevation myocardial infarction(1).
Acute respiratory distress syndrome (ARDS)
An acute, diffuse, inflammatory form of lung injury that is associated with a variety of aetiologies and meets the following criteria: - Within one week of a known clinical insult or new or worsening respiratory symptoms - Bilateral opacities; not fully explained by effusions, lobar/lung collapse or nodules - Respiratory failure not fully explained by cardiac failure or fluid overload - Oxygenation: PaO2/FIO2 ≤ 300mmHg with PEEP or CPAP ≥ 5 cm H_2O(2)
Acute kidney injury (AKI)
- Increase in serum creatinine by ⩾0.3 mg/dl (⩾26.5 µmol/l) within 48 hours, or - Increase in serum creatinine to ⩾1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or - Urine volume <0.5 ml/kg/h for 6 hours(3).
Anaphylactic shock
Signs of massive histamine-mediated vasodilation and maldistribution with a shift of fluid from the intravascular to extravascular space (4)
Benign/non-malignant hematological disease
Benign or premalignant hematological diseases, referring to defects or (congenital or acquired) deficits in the cell lines of red blood cells, platelets or coagulation factors. *Including*: sickle cell disease, hemophilia, essential thrombocythemia, polycythemia, hemochromatosis, aplastic anemia
Bone marrow failure
Decreased blood cell production resulting in a pancytopenia defined as: Hb < 13.5 g/dl (8.4 mmol/L) for males or < 12 g/dL (7.5 mmol/L) for females AND Platelet count< 150 x 10^9 /L AND leukocytes < 4 x 10^9/L (decreased number in all types)
Cardiogenic shock
Shock, primarily caused by a critical reduction of the heart's pumping capacity, caused by systolic or diastolic dysfunction leading to a reduced ejection fraction or impaired ventricular filling. When available MAP 30 mmHg below the baseline value, cardiac index (CI) < 1.8 L/min/m2 without mechanical or pharmacologic support. (4)
Chronic kidney disease (CKD)
Increased creatinine value > 177 µmol/L (= 2.0 mg/dL). Chronic renal insufficiency must have been recorded prior to the current hospital-admission as a chronic condition (existing > 6 months) (5).
Chronic obstructive pulmonary disease (COPD)
Chronic (over 6 months) usage of bronchodilator drugs or steroids indicated for chronic pulmonary diseases. COPD must have been recorded prior to this current hospital-admission **and** the patient must be using medication indicated for COPD. *Including*: chronic bronchitis, chronic bronchiolitis and emphysema (6).
Disseminated intravascular coagulation (DIC)
ISTH DIC score >5. Use calculator to check if patient fulfills the criteria: https://www.mdcalc.com/isth-criteria-disseminated-intravascular-coagulation-dic
Distributive shock

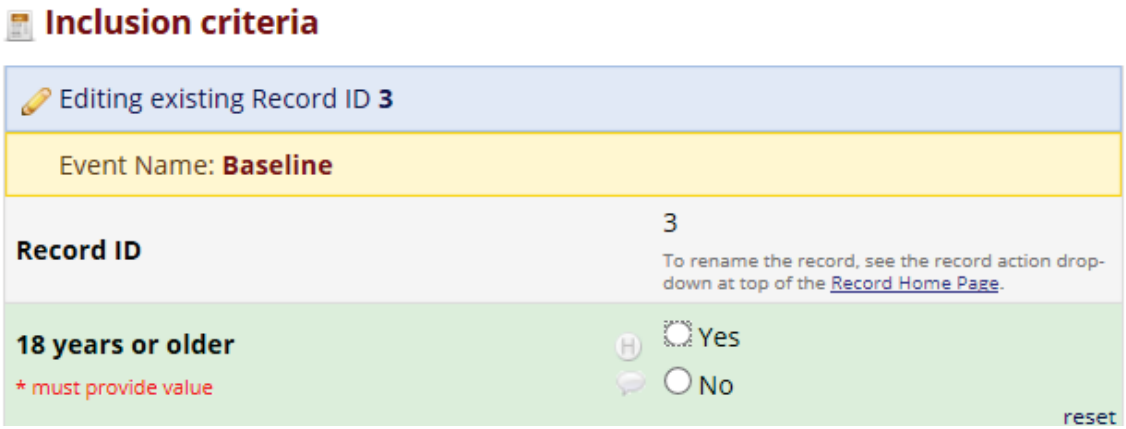
State of relative hypovolemia resulting from pathological redistribution of the absolute intravascular volume, due to loss of vascular tone regulation, volume shifts and/or enhanced permeability of the vascular system. Divided in septic, anaphylactic/anaphylactoid and neurogenic shock. (4)
Failure to wean
Defined as the failure to pass a spontaneous-breathing trial or the need for reintubation within 48 hours following extubation.(7)
Gastro-intestinal bleeding
Significant blood loss via the gastro intestinal tract. Estimated blood loss >200 ml over 24 hours.
Ischemic cerebrovascular accident (iCVA)
Decrease blood flow to a part of the brain resulting in impaired brain function of this area caused by thrombosis, an embolus or systemic hypoperfusion
Heart failure
Ejection fraction <40% **AND** heart failure must have been recorded prior to this current hospital-admission as a chronic condition (existing > 6 months) **OR** patient must be using drugs prescribed with the indication heart failure.
Hemorrhagic cerebrovascular accident (hCVA)
Includes intraparenchymal, intraventricular and subarachnoidal hemorrhages.
Heparin induced thrombocytopenia (HIT)
Thrombocytopenia due to recent administration of heparin (confirmed with lab testing).
Hypovolemic shock
Condition of inadequate organ perfusion caused by (acute) loss of intravascular volume, resulting in decreased cardiac preload. It can be divided in hemorrhagic shock, traumatic hemorrhagic shock, hypovolemic shock and traumatic hypovolemic shock.
Hematological malignancy
Neoplasms, derived from the myeloid or lymphoid cell lines, eg leukemia and lymphoma.
Idiopathic thrombocytopenic purpura (ITP)
Isolated low platelet count with normal bone marrow in the absence of another cause of the thrombocytopenia.
Liver failure
(sub) acute or chronic liver injury associated with development of a coagulopathy of liver etiology (defined as INR > 1.5), and clinically apparent altered level of consciousness due to hepatic encephalopathy
Mechanical ventilation, invasive
Ventilation via an orotracheal tube or tracheostomy.
Mechanical ventilation, non-invasive
Ventilation via a face or a nasal mask. Includes CPAP (continuous positive airway pressure) and BiPAP (Bilevel Positive Airway Pressure)
Neurogenic shock
State of imbalance between sympathetic and parasympathetic regulation of cardiac action and vascular smooth muscle. (4)
Obstructive shock
Condition caused by the obstruction of the great vessels or the heart itself (e.g. tamponade or pulmonary embolism).(4)
Renal replacement therapy (RRT)
Therapy that replaces the normal blood-filtering function of the kidneys, including dialysis, hemofiltration, hemodiafiltration and peritoneal dialysis.
Retinal bleeding
Bleeding in the retina confirmed by an ophthalmologist.

Sepsis
Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Clinical criteria: Suspected or documented infection and an acute increase of ≥2 SOFA points.(8)
Septic shock
Sepsis and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation. (8)
Shock
Shock is classified as, hypovolemic, cardiogenic, obstructive or distributive, and has been defined as a pathophysiological state in which there is an inadequate supply or inappropriate use of metabolic substrate (particularly oxygen) by peripheral tissues.(9)
Solid malignancy
Non-hematologic malignancy, including carcinoma and sarcoma. Does not include lymphoma.
Thrombotic thrombocytopenic purpura (TTP)
A thrombotic micro-angiopathy due to decreased ADAMTS13 activity. Resulting in fever, changed mental status, thrombocytopenia, reduced kidney function and/or hemolytic anemia.
Veno-arterial extracorporeal membrane oxygenation
Extracorporeal membrane oxygenation indicated as a bridging therapy for potentially reversible isolated cardiac or combined cardiopulmonary failure, refractory to conventional therapy. *Including*: triple cannulation therapies, such as veno-veno-arterial ECMO (VVA-ECMO) and veno-arterio-venous ECMO (VAV-ECMO).(10)
Veno-venous extracorporeal membrane oxygenation
Extracorporeal membrane oxygenation indicated as a bridging therapy for potentially reversible pulmonary failure, refractory to conventional therapy. *Including*: extracorporeal carbon dioxide removal ($ECCO_2R$)(10)

STEP 1. INCLUSION PHASE

Every participating center includes during one week. In this week, all newly admitted patients on the ICU will be included and followed until discharge and/or 28 days. Newly admitted patients include patients admitted from the emergency room, operation theater, a general ward or another hospital. Patients can only be included in the study *once*.

Discharge is defined as discharge from the ICU to a general ward/another hospital/home **or** if the patient dies at the ICU during the 28 day follow up.



Example
Miss A, 38 years, is admitted to the ICU with a severe pneumonia at the 6th of July 2020, in the week your hospital is in charge for patient inclusion. She recovers quickly and is discharged at the 9th of July to the general ward. However, in the general ward her condition is deteriorating and she is readmitted to the ICU.

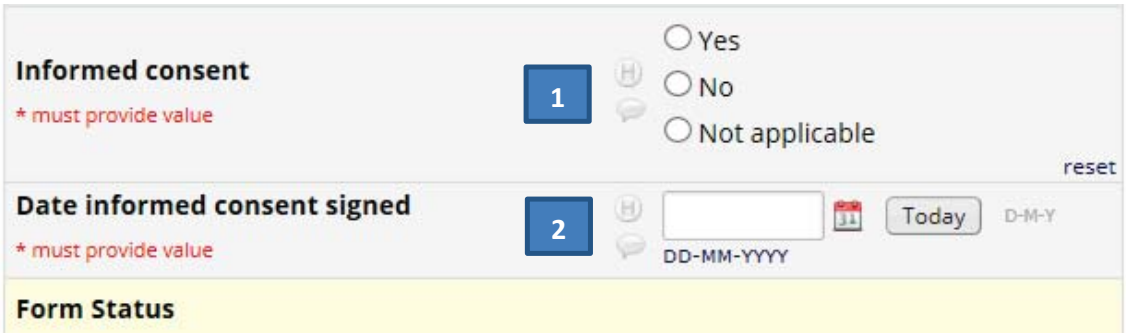
Q: Does Miss A has to be included in the *InPUT* as a new case?
A: No, since Miss A is already included in the *InPUT study* once, it is not possible to create a new case for the *InPUT study*.

Q: If the 6th of July is day 0, does the 9th of July count as the 3rd day, meaning that data collection continues from this day until the 28th day (4th of August) of follow up?
A: No, when a patient is included once, and has been discharged and readmitted, this readmission does not count as a continuation of the initial admission. It is not necessary to collect further data.
However, for the initial inclusion data for day 28 is obligatory for Miss A.

Informed consent

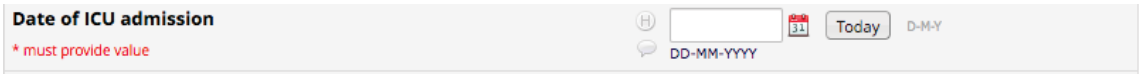
In the different participating countries, different rules apply, e.g. for informed consent to be a participant in this non-interventional, prospective study. In the following question, you can fill in if informed consent is required (1).

In case informed consent is required at your center to include patients in the study, please fill in the date when the informed consent form was signed (2).

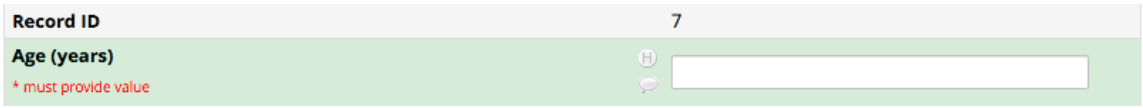


In case of deferred consent, you can also fill in this form later.

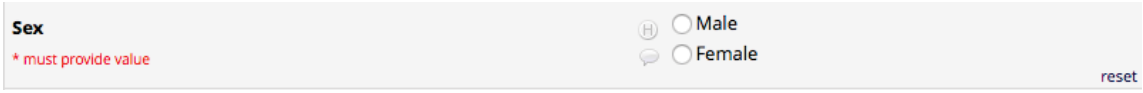
STEP 2. DEMOGRAPHICS



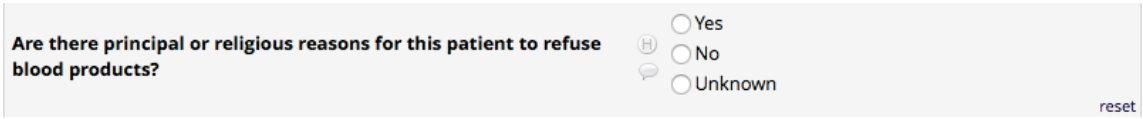
Date of the day of admission to the ICU, noted as **DD**-**MM**-YYYY



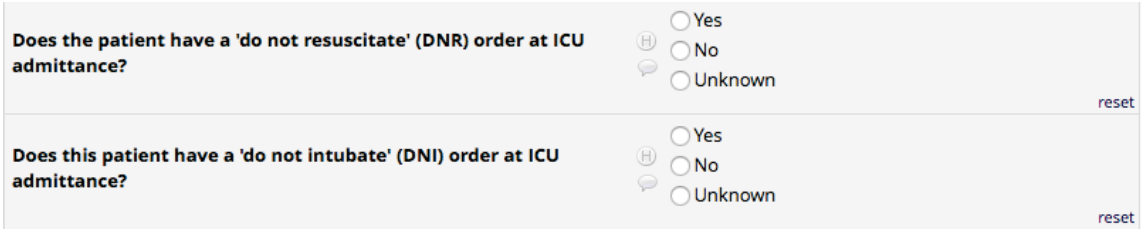
Age in years at the day of admission to the ICU



Sex of the admitted patient



For some patients, there might exists reasons not to want to receive blood products, such as religious or cultural grounds. This therefore can lead to bias in a selective patient population. If it is noted, by the patient or in the patient record, that the patient does not want to receive blood products, please note.



At the day of admission to the ICU, is there notice of a do not resuscitate or do not intubate order? Do not resuscitate includes decided by the patient himself, already noted in the system, or decided by the clinician. The same accounts for do not intubate. Do not intubate does only refer to invasive ventilation via an orotracheal tube or tracheostomy.

What is the referring specialism?	○ Cardiology ○ Cardiothoracic surgery ○ Gastroenteral surgery ○ Gynecology ○ Internal medicine ○ Neurology ○ Neurosurgery ○ Orthopedic surgery ○ Pulmonology ○ Surgery ○ Trauma surgery ○ Urology ○ Other

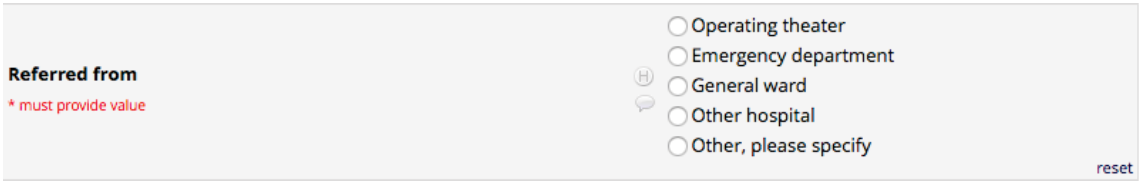
Here, we ask for the specialism for which the patient was admitted to the ICU. In case of multiple specialisms involved with the admission of the patient, please choose the specialism that was the leading clinician in the hospital admission.

Type of admission * must provide value	○ Elective ○ Emergency reset

In this question a distinction is made between an **elective** or **emergency**/urgent admission type. Elective admission to the ICU includes admissions to the ICU that are planned procedures in the specific center, such as after surgery. Emergency admission includes unplanned admission to the ICU from the emergency room/operating theater/general ward/another hospital with urgency.

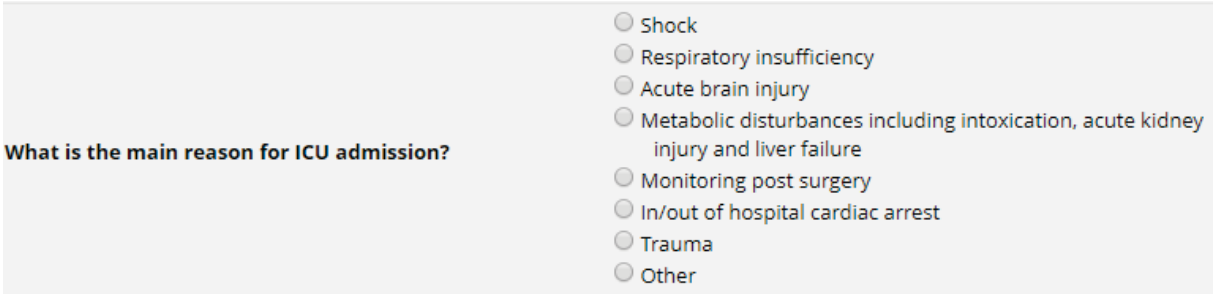
For example: **Elective**
1) a patient scheduled for a valve replacement is admitted to the ICU after the surgery.
2) a patient scheduled for a large esophageal surgery is admitted to the ICU after the surgery.

For example: **Emergency**
1) a patient in respiratory distress in the emergency room has to receive (non) invasive respiratory supportive therapy to insure a safe and efficient airway and breathing.
2) a patient is admitted to the emergency room after being in a multi-trauma car versus car accident. Patient is admitted to the ICU for further observation and optimal treatment.
3) a patient with a hematological malignancy develops a neutropenic sepsis after stem cell transplantation. He is admitted to the ICU for optimal treatment and organ support.

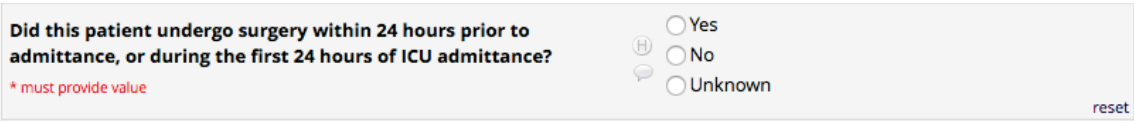


The location of which the patient was referred to the ICU. This refers to the most recent location where the patient was located, before admission to the ICU took place.

For example:
1) a patient in respiratory distress is admitted by the EMT to the emergency rooms. Patient is intubated and is referred to the ICU. **Referred from = emergency department**
2) a patient is admitted to the emergency rooms after he fell from a motor bike. Imaging shows a ruptured spleen, after which the patient undergoes a splenectomy. After surgery patient is admitted to the ICU. **Referred from = operating theater**
3) a patient is transferred from a regional hospital to your center for expertise. After admission to the general ward, the patient develops a cardiogenic shock and has to receive hemodynamic support. Therefore, the patient is admitted to the ICU. **Referred from = general ward**



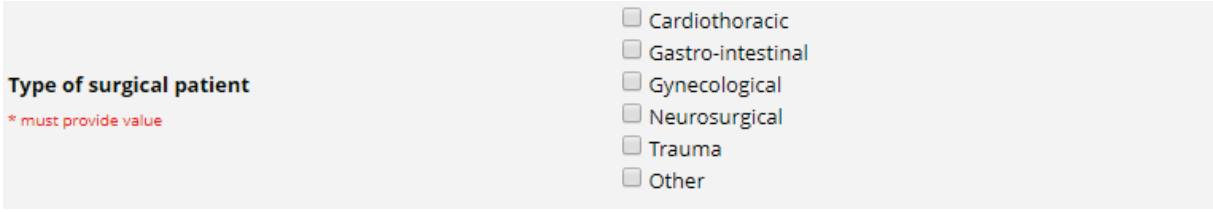
The main reason of admission to the ICU regards the main problem or organ system that is in need of support offered at the ICU. This however is **not** necessarily the same indication as the reason for hospital admission itself. In case of multiple diseased organ tracts, the tract resulting in the highest risk of morbidity or mortality is the main indication of admission.



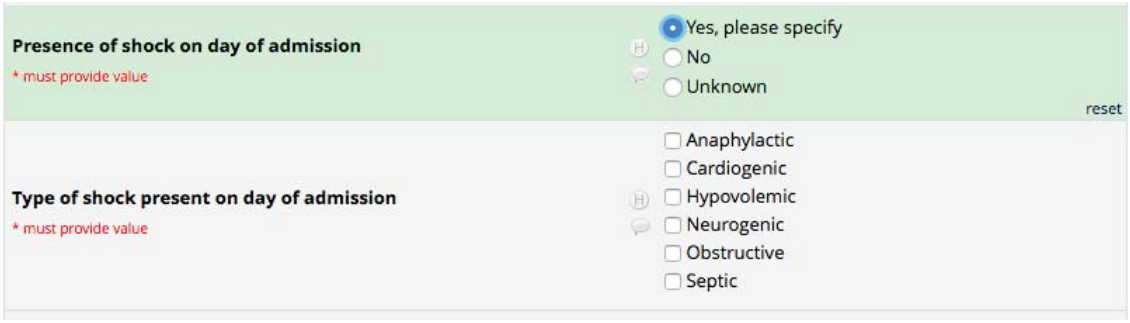
In this question, we refer to if surgery was performed on the patient within 24 hours **before** ICU admission up and until 24 hours **of** ICU admission (t = -24 hours up and until t = + 24 hours). This surgery can be performed within the current hospital where ICU admission takes place, or the referring hospital. It is regardless the size and time of the surgery. Surgery was performed in one of the following locations:

- Operation theater
- Emergency room
- Outside the hospital, in case of an emergency event.

It is regardless the type, size and amount of time that was spent to perform the surgery.



Please specify what type of surgery was performed on this patient.

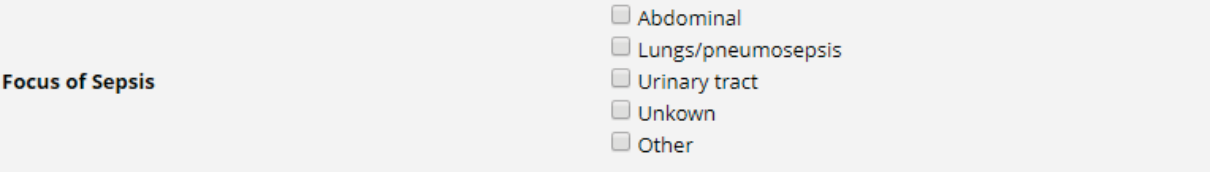


Was shock present at the day of ICU admission?
Shock has been defined as a pathophysiological state in which there is an inadequate supply or inappropriate use of metabolic substrate (particularly oxygen) by peripheral tissues.(9)

In case shock was present at the day of ICU admission, you will be redirected to a second question regarding the type of shock. If multiple types or shock are present, you are able to tick multiple boxes. The types of shock are defined as:

- Anaphylactic – massive histamine-mediated vasodilation and maldistribution with a shift of fluid from the intravascular to extravascular space (4).
- Cardiogenic – Shock, primarily caused by a critical reduction of the heart's pumping capacity, caused by systolic or diastolic dysfunction leading to a reduced ejection fraction or impaired ventricular filling. When available, MAP 30 mmHg below the baseline value, cardiac index (CI) < 1.8 L/min/m2 without mechanical or pharmacologic support. (4)
- Hypovolemic – condition of inadequate organ perfusion caused by (acute) loss of intravascular volume, resulting in decreased cardiac preload. It can be divided in hemorrhagic shock, traumatic hemorrhagic shock, hypovolemic shock and traumatic hypovolemic shock (4).
- Neurogenic - State of imbalance between sympathetic and parasympathetic regulation of cardiac action and vascular smooth muscle.(4)
- Obstructive – condition caused by the obstruction of the great vessels or the heart itself. (4)
- Septic – sepsis which is associated with hypotension and perfusion abnormalities despite adequate fluid resuscitation. Therefore, vasopressor therapy is needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation. (8)

In case of septic shock you will redirected to another question to specify the source. Multiple answers are possible. If source is not yet know please fill in "Unknown"



At the day of admission, we ask for the APACHE IV or the EuroSCORE. In case of a non-cardiothoracic surgical patient, please fill in the APACHE IV score.

Please fill in the highest APACHE IV score or EuroSCORE on the day of admission to the ICU. In case another version of the APACHE is used in your center, please calculate the APACHE IV score by using the following link:

https://intensivecarenetwork.com/Calculators/Files/Apache4.html

In case the main indication of admission to the ICU is cardiothoracic surgery (e.g. post-cardiothoracic surgery), please choose EuroSCORE. If the EuroSCORE is not calculated by the electronic patient record, please calculate by using the following link: …
http://www.euroscore.org/calc.html

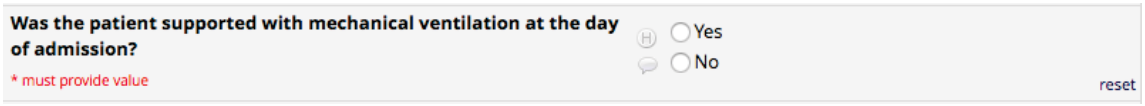
Relevant comorbidities * must provide value	☐ Acute coronary syndrome ☐ Benign hematological disease ☐ Chronic kidney failure ☐ Chronic obstructive pulmonary disease ☐ Heart failure, ☐ Hematologic malignancy ☐ Liver failure ☐ Solid tumor ☐ Organ transplant ☐ Bone marrow transplant ☐ Other, please specify ☐ None

Comorbidities present on the day of admission to the ICU. In case of multiple comorbidities, you are able to tick multiple boxes. A comorbidity must be present for at least 3 months or more, or have to be noted in the (electronic) patient file before.
They are defined as follows:

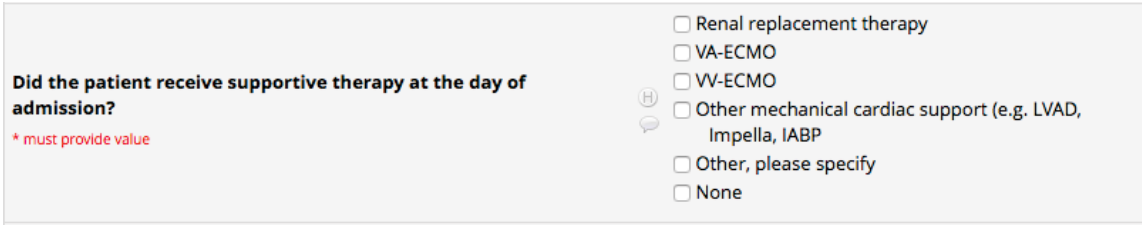
- **Acute coronary syndrome** – A group of clinical symptoms compatible with acute myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina to non-ST-segment elevation myocardial infarction to ST-segment elevation myocardial infarction[1].
  Including: myocardial infarction (**not** being the indication of the current hospital admission), instable angina pectoris.
- **Benign/non-malignant hematological disease** – Benign or premalignant hematological diseases, referring to defects or (congenital or acquired) deficits in the cell lines of red blood cells, platelets or coagulation factors. *Including*: sickle cell disease, hemophilia, essential thrombocythemia, polycythemia, hemochromatosis, aplastic anemia
- **Chronic kidney disease** – Increased creatinine value > 177 μmol/L (= 2.0 mg/dL). Chronic renal insufficiency must have been recorded prior to the current hospital-admission as a chronic condition (existing > 6 months).[4]
- **Chronic obstructive pulmonary disease** – Chronic (over 6 months) usage of bronchodilator drugs or steroids indicated for chronic pulmonary diseases. COPD must have been recorded prior to this current hospital-admission **and** the patient must be using medication indicated for COPD.
  Including: chronic bronchitis, chronic bronchiolitis and emphysema.[5]
- **Heart failure** – Ejection fraction <40% **AND** heart failure must have been recorded prior to this current hospital-admission as a chronic condition (existing > 6 months) **OR** patient must be using drugs prescribed with the indication heart failure.
- **Hematological malignancy** – Neoplasms, derived from the myeloid or lymphoid cell lines, e.g. leukemia and lymphoma.
- **Liver failure** – (sub) acute or chronic liver injury associated with development of a coagulopathy of liver etiology (defined as INR > 1.5), and clinically apparent altered level of consciousness due to hepatic encephalopathy
- **Solid tumor** – Non-hematologic malignancy, including carcinoma and sarcoma. Does not include lymphoma.

- **Organ transplant** – Patient currently has a donor organ. Does not include bone marrow transplant.
- **Bone marrow transplant** – Patient received a bone marrow transplant in the past.
- **Other, please specify** – (chronic) comorbidities or preexistent diseases resulting in deficits or decreased amount of coagulation factors, platelets and hemoglobin.
- **None** – no comorbidities that can result in deficits or decreased amount of coagulation factors, platelets and hemoglobin are present.

Chronic is defined as existing over 6 months **or** noted in the patient records from a previous outpatient clinic visit or hospital admission.



Presence of mechanical ventilation via a tube at the start of ICU admission, including nasotracheal intubation, orotracheal intubation or the presence and active and indicated use of a tracheostomy tube. Patient was already intubated prior to ICU admission, for example in the emergency room or operating theater. Does not include non-invasive mechanical ventilation, such as high flow nasal oxygen (HFO) or non-invasive ventilation (NIV)



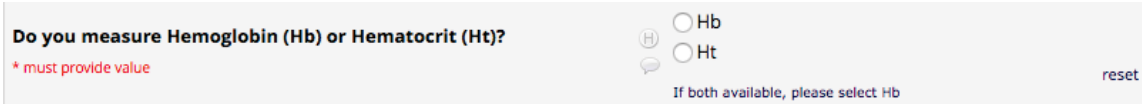
Presence of supportive therapy at the start of ICU admission. Supportive therapy was already present at the moment of ICU admission. Definitions of supportive therapies are as follows:

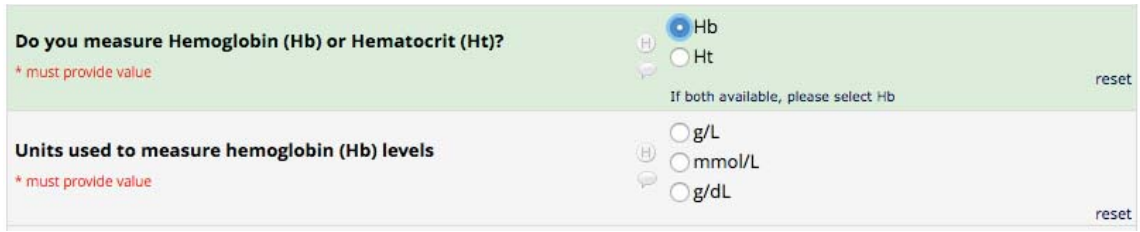
- **Renal replacement therapy** – Therapy that replaces the normal blood-filtering function of the kidneys, including dialysis, hemofiltration, hemodiafiltration and peritoneal dialysis.
- **Veno-arterial extracorporeal membrane oxygenation** – extracorporeal membrane oxygenation indicated as a bridging therapy for potentially reversible isolated cardiac or combined cardiopulmonary failure, refractory to conventional therapy.
  Including: triple cannulation therapies, such as veno-veno-arterial ECMO, veno-arterio-venous ECMO.
- **Veno-venous extracorporeal membrane oxygenation** – extracorporeal membrane oxygenation indicated as a bridging therapy for potentially reversible pulmonary failure, refractory to conventional therapy.
  Including: extracorporeal carbon dioxide removal ($ECCO_2R$)

- **Other mechanical cardiac support** – defined as preexisting mechanical cardiac support at the time of hospital admission or admission to the ICU.
  Including: Berlin heart, bi-ventricular assisting device (BIVAD), cardiac pacemaker, cardiopulmonary bypass, intra-aortic balloon, left ventricular assisting device (LVAD), percutaneous ventricular assist device (PVAD), right ventricular assisting device (RVAD).
- **None** – no supportive therapy was present at the moment of ICU admission.

The following questions regards the laboratory values and its units that are measured during an ICU admission and are relevant to possible transfusion of blood products.

PLEASE NOTE
It is mandatory to fill in these questions. The choices made in these questions will be linked to the further questions in the daily and transfusion questionnaires. It is essential that these questions are filled in prior to completing daily and transfusion questionnaires.



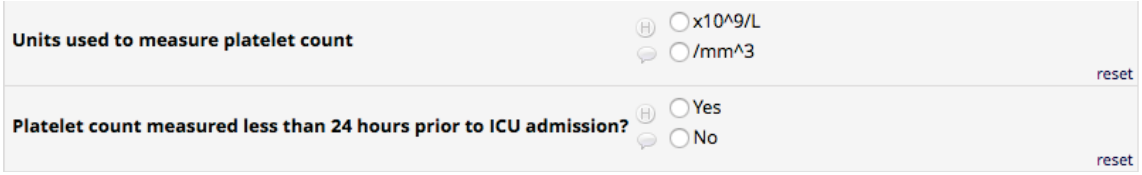


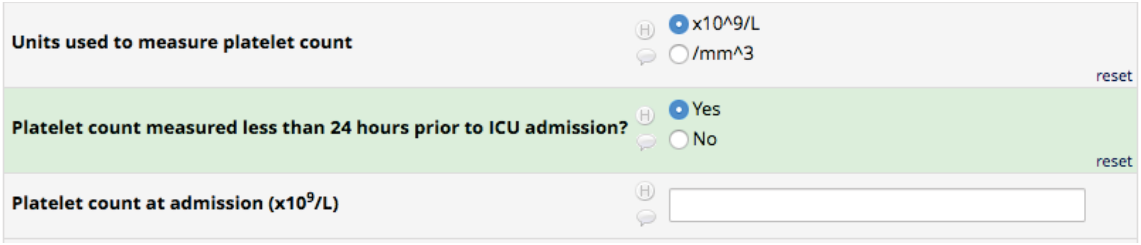
If both hemoglobin and hematocrit (Ht) values are available, please fill in Hb. In the following questions only this unit will be used. It is essential you fill in the unity you use. Otherwise, you won't be able to fill in the pre transfusion and post transfusion hemoglobin values in the transfusion questionnaires.

Hb or Ht at admission is defined as an Hb or Ht value measured within 24 hours prior to ICU admission.

For example:
1) a patient is admitted for surveillance after cardiothoracic surgery. Only a hemoglobin levels is available from three days earlier. In this case you fill in **NO** hb/ht value measured less than 24 hours prior to surgery.

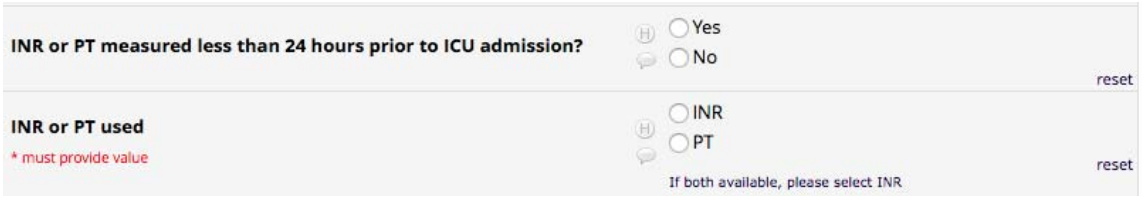
2) a patient is admitted for surveillance after cardiothoracic surgery. Multiple Hb values are measured before and during surgery prior to ICU admission. Hb at admission in this case is the last Hb value prior to ICU admission.





It is essential you fill in the unity you use. Otherwise, you won't be able to fill in the pre- and post transfusion platelet count in the transfusion questionnaire.

Platelet count at admission is defined as a platelet count measured within 24 hours prior to ICU admission



If both INR and PT values are available, please fill in INR.

INR or PT at admission is defined as an INR or PT measured within 24 hours prior to ICU admission

aPTT at admission is defined as an aPTT measured within 24 hours prior to ICU admission

STEP 3. DAILY QUESTIONNAIRE: DAY 0 UP TO DAY 28

This questionnaire will be filled in daily:

- Starting with the admission day itself as day 0;
- Up and until to a maximum of 28 days of ICU admission;
- In case the patient is discharged before the 28th day of ICU admission, data will be collected as long as the patient is located at the ICU, and the extra form regarding patient outcome ("day 28") has to be filled in.
- In case the patient is deceased (dies) before the 28th day of ICU admission, data will be collected as long as the patient is alive, and the form regarding patient outcome ("day 28" has to be filled in);
- In case the patient is discharged before the 28th day of ICU admission, and is readmitted to the ICU within the period of patient inclusion, no further data collection will occur except the outcome data noted in "day 28" for the patient as was the case for the primary admission.

Here we ask you to fill in the day since admission. You can choose to either fill in only the day number, or the date as well. The latter can function as a tool to help yourself calculate with the dates, and as a way that we can correct a miscalculation in the day since admission.
It also has to be filled in for the admission day itself!

Please note that

- **Day 0** is defined as the **day of admission to the ICU**. This is the calendar day, beginning at 00:00 and ending at 23:59. Day 0 can thus have a duration varying from 1 minute up to 24 hours.
- **Day 1** is the calendar day following the initial day of admission to the ICU.
- **Day 2** is the calendar day following the 1st day after admission to the ICU.

Etc. up to and including day 28

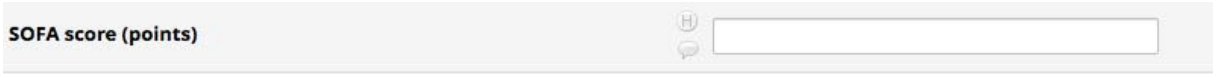
Estimated blood loss in milliliters (mL) during the calendar day of ICU admission. This blood loss includes:

- Estimated blood loss during surgery or intervention;
- Estimated blood loss caused by an iatrogenic complication (e.g. hemothorax after placement of a central venous catheter);

- Estimated blood loss caused by a disease-related complicating (e.g. gastro-intestinal blood loss after a bleed from an gastric or duodenal ulcer);
- Estimated blood loss of drains.

This blood loss does **not** include/the following blood loss is **excluded**:

- Estimated blood loss caused iatrogenic due to (repeated) blood samples, blood gasses or blood cultures.



SOFA-score at the day of data collection during the ICU stay. This SOFA score is calculated in the electronic patient records or can be calculated by hand using the following link:

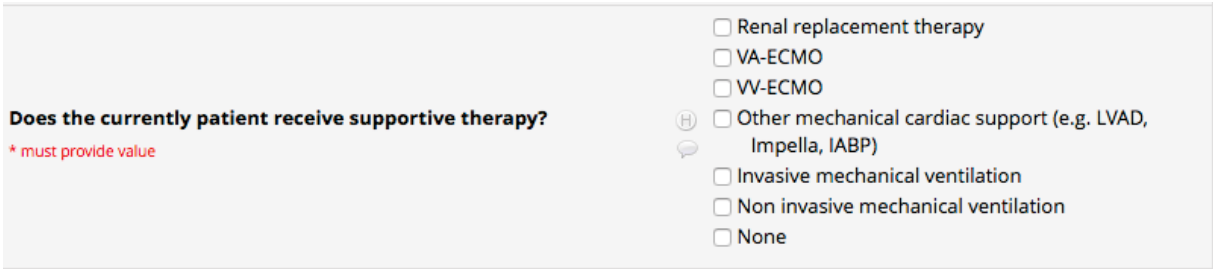
https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score

Daily underlying medical problems need to be scored. Please score each problem which was present on this calendar day.

- **Acute coronary syndrome (ACS)** – A group of clinical symptoms compatible with acute myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina to non-ST-segment elevation myocardial infarction to ST-segment elevation myocardial infarction[1].
- **Acute respiratory distress syndrome (ARDS)** - An acute, diffuse, inflammatory form of lung injury that is associated with a variety of etiologies and meets the following criteria:
  - Within one week of a known clinical insult or new or worsening respiratory symptoms
  - Bilateral opacities; not fully explained by effusions, lobar/lung collapse or nodules
  - Respiratory failure not fully explained by cardiac failure or fluid overload
  - Oxygenation: PaO2/FIO2 ≤ 300mmHg with PEEP or CPAP ≥ 5 cm H2O[2]
- **Acute kidney injury (AKI)** – defined as:
  - Increase in serum creatinine by ⩾0.3 mg/dl (⩾26.5 µmol/l) within 48 hours, or
  - Increase in serum creatinine to ⩾1.5 times baseline, which is known or presumed to have

occurred within the prior 7 days, or
- Urine volume <0.5 ml/kg/h for 6 hours[3].

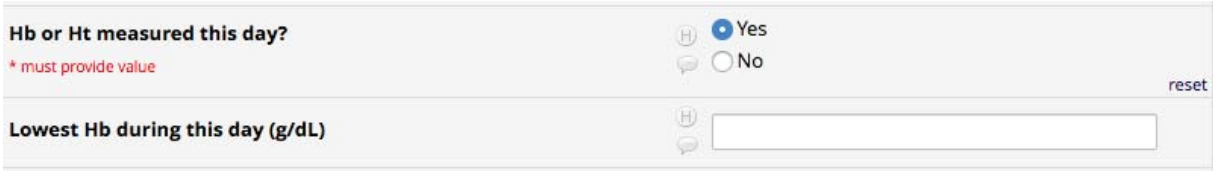
- **Bone marrow failure**: Decreased blood cell production resulting in a pancytopenia defined as:
    - Hb < 13.5 g/dl (8.4 mmol/L) for males or < 12 g/dL (7.5 mmol/L) for females
    - AND Platelet count< 150 x 109 /L
    - AND leukocytes < 4 x 109/L (decreased number in all types)
- **Failure to wean** – defined as the failure to pass a spontaneous-breathing trial or the need for reintubation within 48 hours following extubation.[6]
- **Ischemic cerebrovascular accident** – Decrease blood flow to a part of the brain resulting in impaired brain function of this area caused by thrombosis, an embolus or systemic hypoperfusion
- **Hemorrhagic cerebrovascular accident** – Includes intraparenchymal, intraventricular and subarachnoidal hemorrhages.
- **GI-bleeding** – Significant blood loss via the gastro intestinal tract. Estimated blood loss >200 ml over 24 hours.
- **Liver failure** - (sub) acute or chronic liver injury associated with development of a coagulopathy of liver etiology (defined as INR > 1.5), and clinically apparent altered level of consciousness due to hepatic encephalopathy
- **Retinal bleeding** – Bleeding in the retina confirmed by an ophthalmologist
- **Sepsis** - life-threatening organ dysfunction caused by a dysregulated host response to infection. Clinical criteria: suspected or documented infection and an acute increase of ≥2 SOFA points.[7]



The patient receives supportive therapy, as well the newly initiated therapy as the supportive therapy that was already received by the patient.

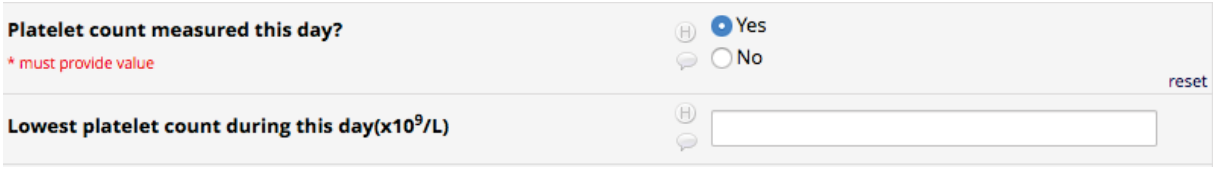
Definitions can be found in the following paragraphs:

1) Abbreviations & definitions
2) Patient demographics: supportive therapy



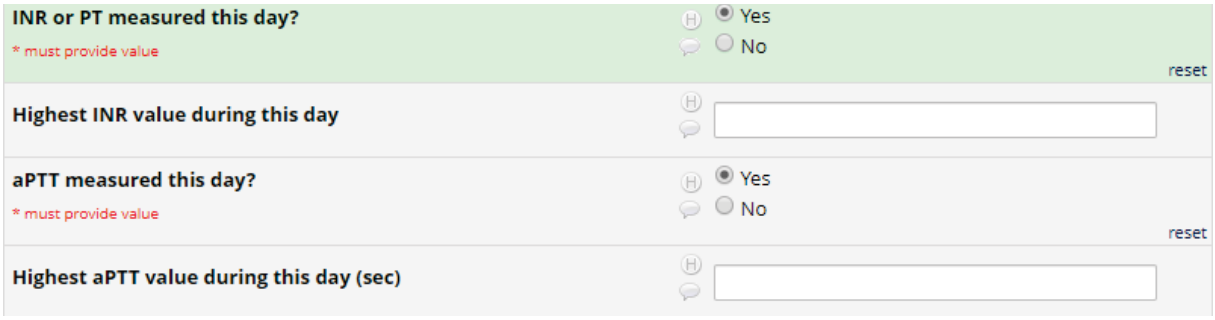
Fill in the lowest hemoglobin value measured this calendar day.

!! Please note **you have to filled in the unit that is used in your center to express hemoglobin level to be able to fill in a daily value of hemoglobin.**

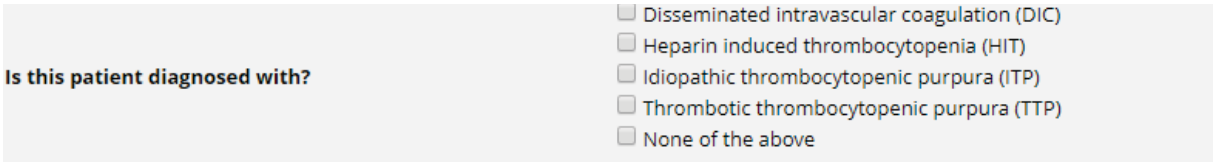


Fill in the lowest platelet count measured this calendar day.

!! Please note **you have to filled in the unit that is used in your center to express platelet count to be able to fill in a daily value of platelet count.**



If INR/PT and/or aPTT are measured fill in the highest measured value this calendar day.

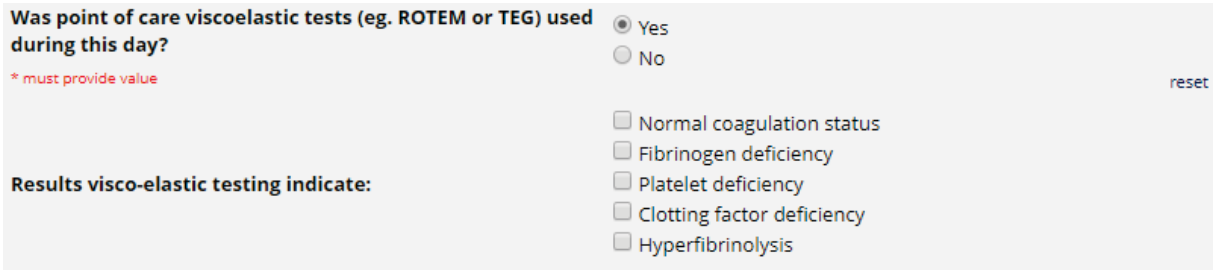


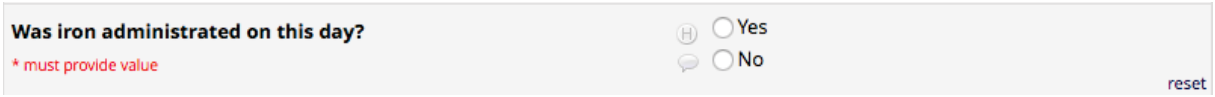
If the platelet count is lower than 150 x 10^9/L you will be redirected to this question:

Definitions:

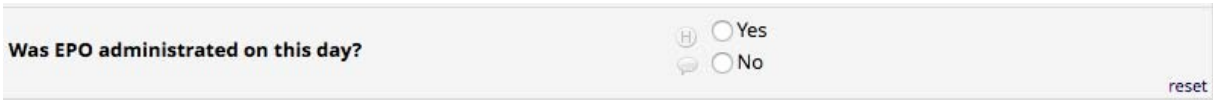
- **Disseminated intravascular coagulation (DIC)** – ISTH DIC score >5. Use calculator to check if patient fulfills the criteria: https://www.mdcalc.com/isth-criteria-disseminated-intravascular-coagulation-dic

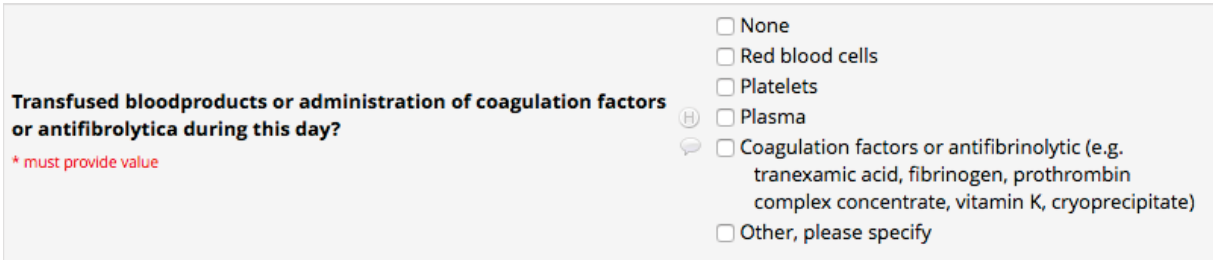
- **Heparin induced thrombocytopenia (HIT)** – thrombocytopenia due to recent administration of heparin (confirmed by lab testing).
- **Idiopathic thrombocytopenic purpura (ITP)** – Isolated low platelet count with normal bone marrow in the absence of another cause of the thrombocytopenia.
- **Thrombotic thrombocytopenic purpura (TTP)** – A thrombotic microangiopathy due to decreased ADAMTS13 activity. Resulting in fever, changed mental status, thrombocytopenia, reduced kidney function and/or hemolytic anemia.





Includes orally and intravenous iron administration.





Please make sure that for each product a separate transfusion questionnaire is completed. Only in case of massive transfusion, one specific form for massive transfusion needs to be filled in.

After filling in a daily questionnaire, the following daily questionnaire can be added by clicking on the ‘plus’/’ add’ sign next to the colored circle.

TRANSFUSION

A 'transfusion event' is defined as:

- Administration or transfusion of blood products or anticoagulation factors

Fill in a separate transfusion questionnaire for each time blood products or drugs are ordered.

For example:
1) a patient is bleeding resulting in a decreased Hb level. Therefore the physician decides this patient needs two units of red cell concentrates. This is **one** transfusion event

2) a patient is bleeding resulting in a decreased Hb level. Therefore the physician decides this patient needs one unit of red cell concentrates. After one unit hemoglobin is measured again. Based on this result the physician orders a new unit. These are **two** transfusion events

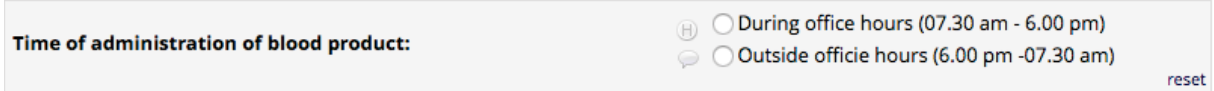
3) a patient with a low Hb level is tachycardic and has an increased lactate level. Therefore the physician decides this patient needs a units of red cell concentrate. After one unit the condition of the patient does not improve. Based on this observation, the physician orders a new unit red cell concentrate. These are **two** different transfusion events

Massive transfusion is defined as:

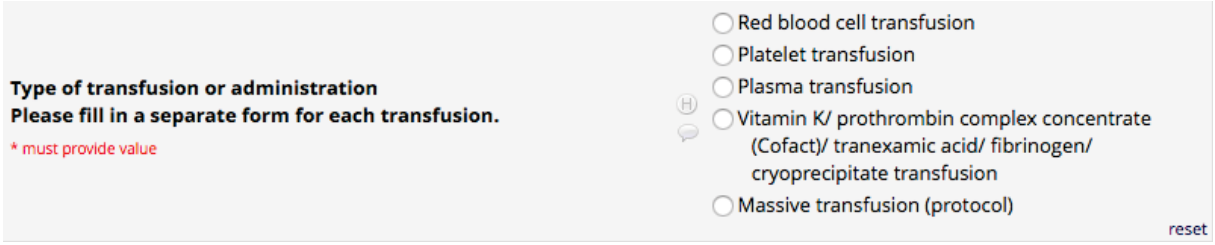
- Activation of a massive transfusion protocol;
- Administration of four or more blood components within 30 minutes in an actively bleeding patient

Please note

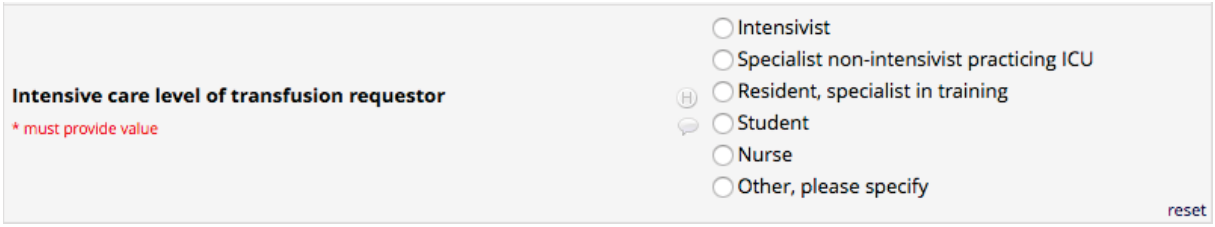
*By choosing a type of transfusion or administration, you will be directed automatically to the questions regarding that type. In this SOP the order of the explanation of the questions therefore does **not** necessarily match the order as found on RedCap.*



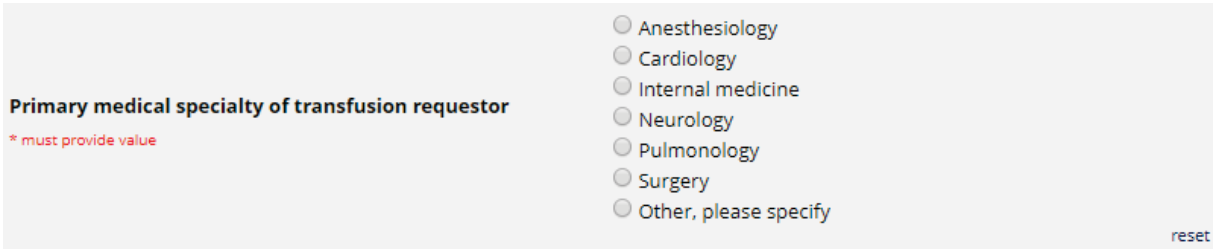
Use the time of start administration of the blood product or drug.



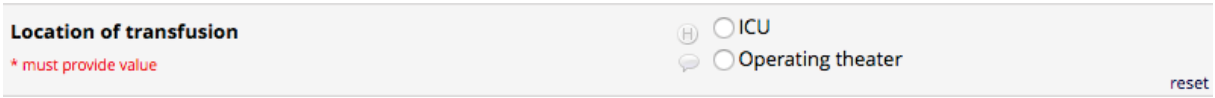
Fill in a separate transfusion questionnaire for each time blood products or drugs are ordered.



The *transfusion requestor* is defined as the medical employee that decided there was an indication for transfusion or administration of anticoagulation factors. This is not necessarily the supervisor or the person who orders the blood product/coagulation factor.



In this question, the primary medical specialty is required. This refers to the primary medical specialization of the transfusion requestor. This can be a specialty of a certified specialist, or, in case of a resident/specialist in training a specialty that is not yet completed.



The location of transfusion is the location where the actual transfusion or administration of blood or coagulation products took place. This does not necessarily have to be the location where the blood or coagulation product was ordered. In case the blood or coagulation product was ordered on a different location than where the product was administered/transfused, the latter is the location that has to be filled in.

For example:
1) A patient admitted to the ICU has a severe anemia, most likely due to acute illness. The resident orders red blood cells, which are transfused an hour later.
Location of transfusion = ICU

2) Since the patient does not improve, a CT-scan is performed with contrast, and an active bleed is found in an abdominal mass. The patient is therefore transferred to the operation theater. The resident of the ICU is asked to already order several blood products, which are later transfused and administered during the surgery.
Location of transfusion = OR

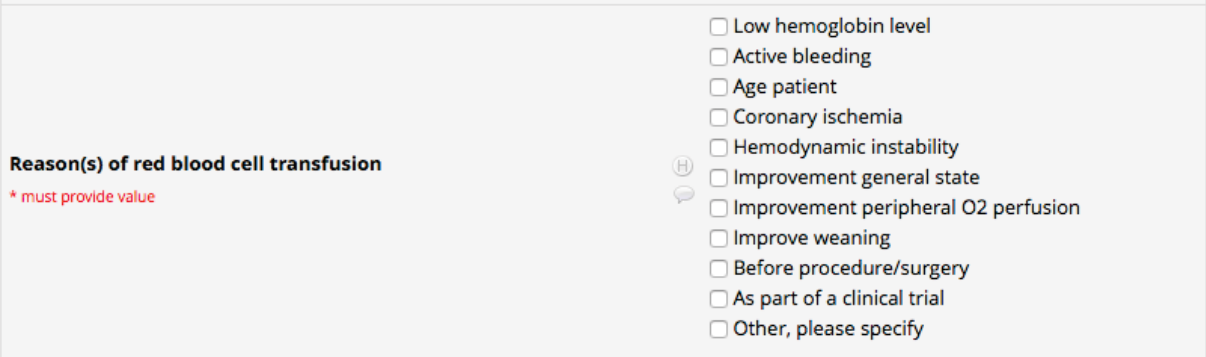
Was the decision to transfuse and/or administer coagulation factors guided by viscoelastic tests (eg. ROTEM, TEG)?

- ○ Yes
- ○ No

reset

* must provide value

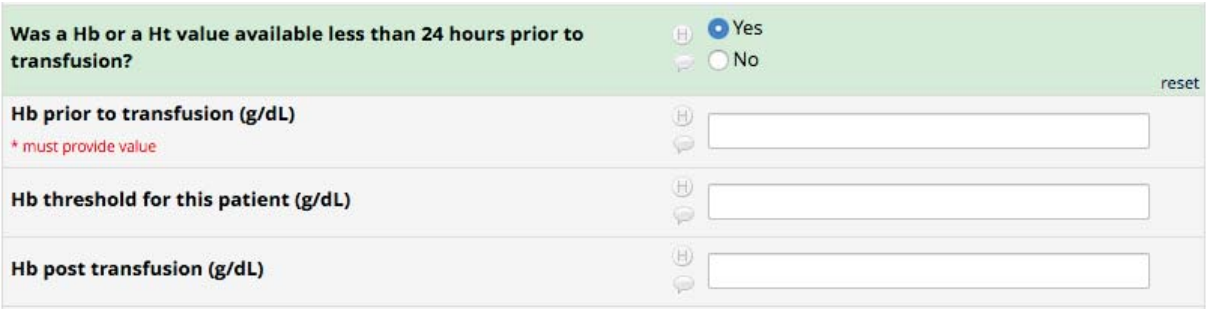
RED BLOOD CELL TRANSFUSION



Multiple factors could contribute to the decision to transfuse. Only fill in the factors that contributed.

For example:
1) a patient receives a red blood cell transfusion because of a low Hb level. Later this day he will undergo surgery. However, this fact did not influence the decision to transfuse. In this case reason of transfusion is “low hemoglobin value”.

2) a patient receives a red blood cell transfusion because of a low Hb level and the surgery he will undergo the next day. In this case reason of transfusion is “low hemoglobin value” AND “before procedure/surgery”.



There are several questions connected to RBC transfusion, regarding the hemoglobin/hematocrit value prior to and after transfusion, and the threshold that was chosen for that certain patient.

The questions will be shown in the laboratory value and unit used in your medical center, as chosen by you in the demographics. Options for laboratory values in RBC transfusion are hemoglobin (in g/dL, mmol/L, g/L) or hematocrit (in L/L).

The hemoglobin/hematocrit **prior to transfusion** is defined as:

- The most recent Hb/Ht value known/measured prior to RBC transfusion within 4 hours prior to the decision to transfuse;

- It is possible for this most recent value that it was measured the calendar day before RBC transfusion was given;
- <24 h

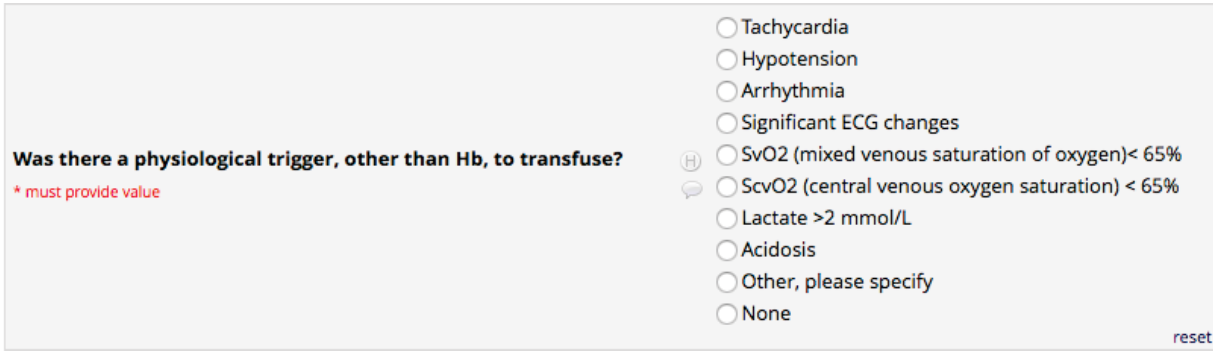
The hemoglobin/hematocrit **post transfusion** is defined as:

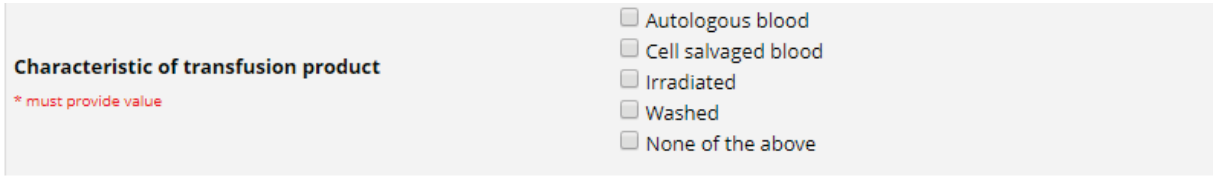
- The first Hb/Ht value measured after RBC transfusion was given (<24 hours after ending transfusion);
- It is possible for this value that this was measured the calendar day after RBC transfusion was given;
- In case this Hb/Ht was measured during transfusion please use the first value after transfusion (<24 hours, otherwise don't fill in value).

The **threshold for this patient** is defined as:

- The threshold for RBC transfusion stated by the medical protocol **or** stated by expert opinion for that certain patient or its patient group;

For example:
1) Due to acute coronary ischemia the physician wants his patient to have an Hb level > 12 g/dL. Therefore he transfuses at an Hb level at 11.5 g/dl. In this case the pre transfusion Hb is 11.5 g/dL and the Hb threshold is 12 g/dL.





Definitions:

- **Autologous blood** – Reinfusion of patients own blood. Blood can be collected either via cell saver during surgery or was donated blood prior to hospital admission.
- **Cell salvaged blood** –Blood collected for patient's own blood lost during or after surgery.

- **Irradiated** – Blood that has been radiated to prevent Transfusion Associated Graft-Versus Host Disease.
- **Washed** – Washed by the bloodbank or laboratory prior transfusion (e.g. in case of severe febrile or anaphylactic reactions on previous blood products).
- **Note:** multiple options are possible

PLATELET TRANSFUSION

Reason of transfusion * must provide value	☐ Active bleeding ☐ Prophylactic (in the absence of an upcoming procedure) ☐ As part of a clinical trial ☑ Upcoming procedure, please specify ☐ Results viscoelastic testing (ROTEM, TEG)
Upcoming procedure wherefore transfusion * must provide value	☐ Abdominal drain placement ☐ Bone marrow biopsy ☐ Cardiac thoracic surgery, ☐ Central venous catheter ☐ General surgery ☐ Lumbar puncture ☐ Neurosurgery ☐ Organ biopsy (liver, kidney) ☐ Thorax drain placement ☐ Tracheostomy ☐ Other, please specify

Multiple reasons may be applicable to the reason to transfuse. If an upcoming procedure was (one of) the reason(s) to transfuse, a new question will appear to specify this procedure.

Was a platelet count available less than 24 hours prior to transfusion?	◉ Yes ○ No reset
Platelet count prior to transfusion (/mm^3) * must provide value	
Platelet target for this patient (/mm^3)	
Platelet count post transfusion (/mm^3)	

There are several questions connected to platelet transfusion, regarding the platelet count prior to and after transfusion, and the threshold that was chosen for that certain patient.

The questions will be shown in the laboratory value and unit used in your medical center, as chosen by you in the demographics. Options for laboratory values in platelet transfusion are a platelet count in 10^9/L or / mm^3

The platelet count **prior to transfusion** is defined as:

- The most recent platelet count known/measured prior to platelet transfusion within 4 hours prior to the decision to transfuse;
- It is possible for this most recent value that it was measured the calendar day before platelet transfusion was given;

The platelet count **post transfusion** is defined as:

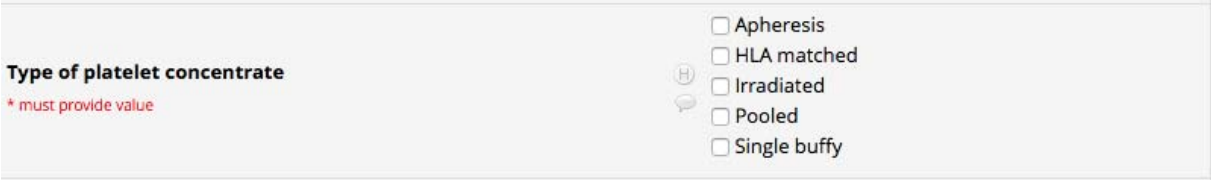
- The first platelet count value measured after platelet transfusion was given(<24 hours after ending transfusion);
- It is possible for this value that this was measured the calendar day after platelet transfusion was given;
- In case this platelet count was measured during transfusion please use the first value after transfusion.

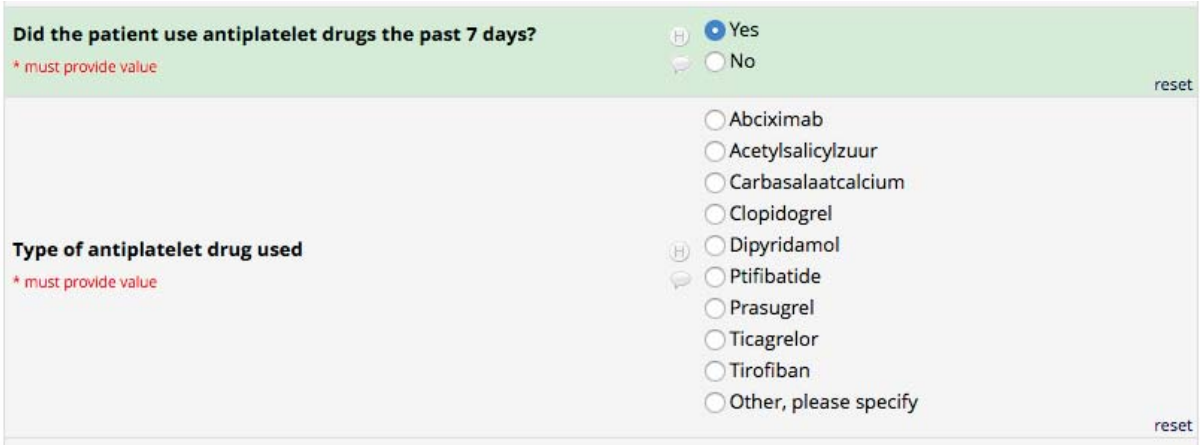
The **threshold for this patient** is defined as:

- The threshold for platelet transfusion stated by the medical protocol **or** stated by expert opinion for that certain patient or its patient group;

For example:
1) Due to retinal bleeding in the past of a patient. The physician aims at a platelet count >40 $x10^9$ /L. Today this patient has a platelet count of 15 $x10^9$ /L. Based on this platelet count he receives a platelet transfusion. In this case the pre transfusion platelet count in this case is 15 $x10^9$ /L and the platelet threshold is 40 $x10^9$ /L

2) A patient with leukemia is admitted to the ICU. No invasive procedures are planned the following days. According to local guidelines the aim for this patient is to keep the platelet count > 10 $x10^9$ /L. Today this patient has a platelet count of 5 $x10^9$ /L. Based on this platelet count he receives a platelet transfusion. In this case the pre transfusion platelet count in this case is 5 $x10^9$ /L and the platelet threshold is 10 $x10^9$ /L





One pooled platelet concentrate is considered to be one unit (even if this product is derived from multiple buffy coats). Two different units, which are both single buffy coat products, are considered as two different units. In the final analysis, this will be corrected.

PLASMA TRANSFUSION

Reason of transfusion * must provide value	☐ Active bleeding ☐ Prophylactic (in the absence of an upcoming procedure) ☐ As part of a clinical trial ☐ Upcoming procedure, please specify ☐ Results viscoelastic testing (ROTEM, TEG)

Multiple reasons are possible.

Reason of transfusion * must provide value	☐ Active bleeding ☐ Prophylactic (in the absence of an upcoming procedure) ☐ As part of a clinical trial ☑ Upcoming procedure, please specify ☐ Results viscoelastic testing (ROTEM, TEG)
Upcoming procedure wherefore transfusion * must provide value	☐ Abdominal drain placement ☐ Bone marrow biopsy ☐ Cardiac thoracic surgery, ☐ Central venous catheter ☐ General surgery ☐ Lumbar puncture ☐ Neurosurgery ☐ Organ biopsy (liver, kidney) ☐ Thorax drain placement ☐ Tracheostomy ☐ Other, please specify

Was a PT or INR available less than 24 hours prior to transfusion?	◉ Yes ○ No reset
INR prior to transfusion * must provide value	
INR target for this patient	
INR post transfusion	

There are several questions connected to plasma transfusion, regarding the coagulation test values prior to and after transfusion, and the threshold that was chosen for that certain patient.

The questions will be shown in the laboratory value and unit used in your medical center, as chosen by you in the demographics. Options for laboratory values in plasma transfusion are prothrombin time (PT, in seconds) or international normalized ratio (INR, a ratio).

The coagulation test **prior to transfusion** is defined as:

- The most recent PT/INR value known/measured prior to plasma transfusion measured within 4 hours prior to the decision to transfuse was made;
- It is possible for this most recent value that it was measured the calendar day before plasma transfusion was given.

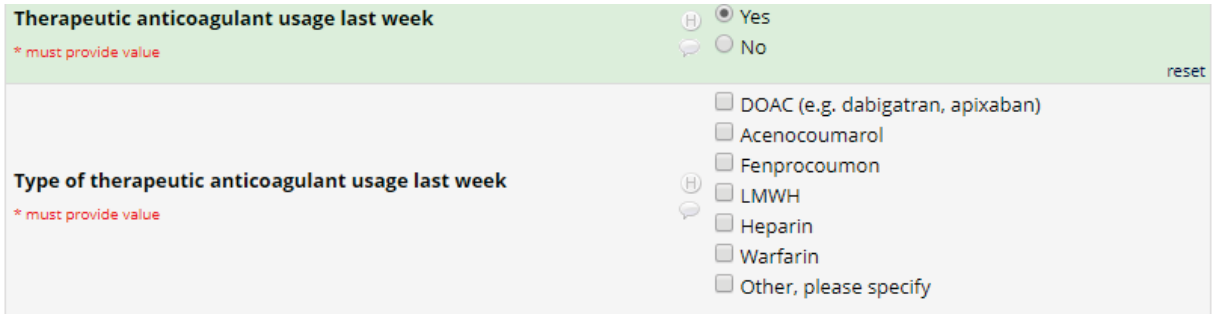
The coagulation test **post transfusion** is defined as:

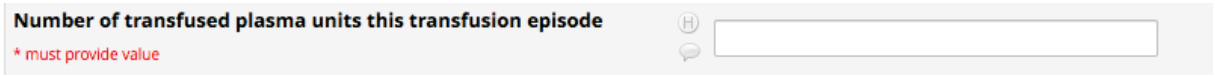
- The first PT/INR value measured after plasma transfusion was given (<24 hours after ending transfusion);
- It is possible for this value that this was measured the calendar day after plasma transfusion was given;
- In case this PT/INR was measured during transfusion please use the first value after transfusion.

The **threshold for this patient** is defined as:

- The threshold for plasma transfusion stated by the medical protocol **or** stated by expert opinion for that certain patient or its patient group;

For example:
1) a patient with an INR of 4 is planned for abdominal surgery. Because the surgeon wants the INR <1.5, this patient receives one unit of plasma. In this case the pre transfusion INR is 4 and the INR threshold is 1.5.





ADMINISTRATION OF VITAMIN K/PROTHROMBIN COMPLEX CONCENTRATE/ FIBRINOGEN/ TRANEXAMIC ACID/ CRYOPRECIPITATE

Type of transfusion or administration **Please fill in a separate form for each transfusion.** * must provide value	○ Red blood cell transfusion ○ Platelet transfusion ○ Plasma transfusion ◉ Vitamin K/ prothrombin complex concentrate (Cofact)/ tranexamic acid/ fibrinogen/ cryoprecipitate transfusion ○ Massive transfusion (protocol) reset
Drug used * must provide value	○ Cryoprecipitate ○ Fibrinogen ○ Prothrombin ○ Tranexamic acid ○ Vitamin K reset

Per drug one transfusion events needs to be completes, unless it was part of a massive transfusion event.

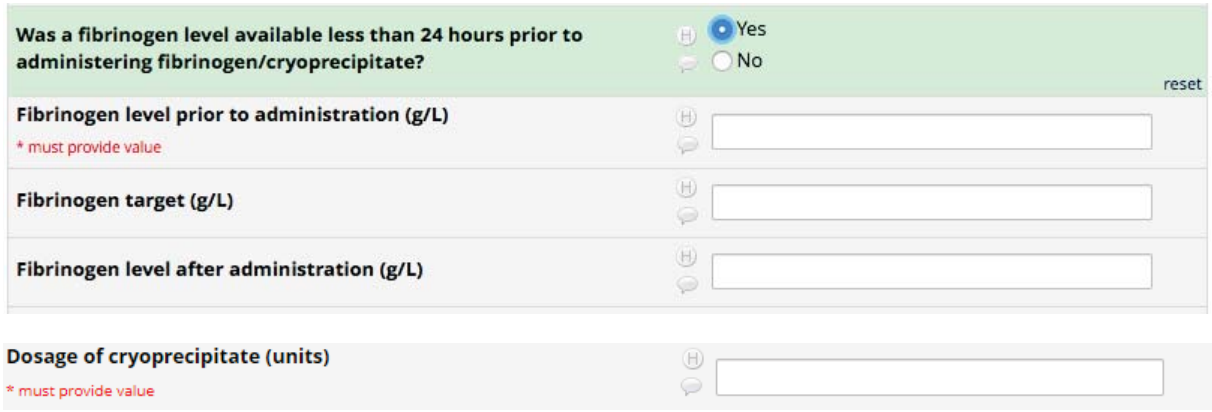
Reason of transfusion * must provide value	☐ Active bleeding ☐ Prophylactic (in the absence of an upcoming procedure) ☐ As part of a clinical trial ☐ Upcoming procedure, please specify ☐ Results viscoelastic testing (ROTEM, TEG)

With the exception of tranexamic acid administration, the following question also has to be filled in.

Therapeutic anticoagulant usage last week * must provide value	◉ Yes ○ No reset
Type of therapeutic anticoagulant usage last week * must provide value	○ DOAC ○ Acenocoumarol ○ Fenprocoumon ○ LMWH ○ Heparin ○ Warfarin ○ Other, please specify reset
Was anticoagulant usage a trigger to transfuse? * must provide value	○ Yes ○ No reset

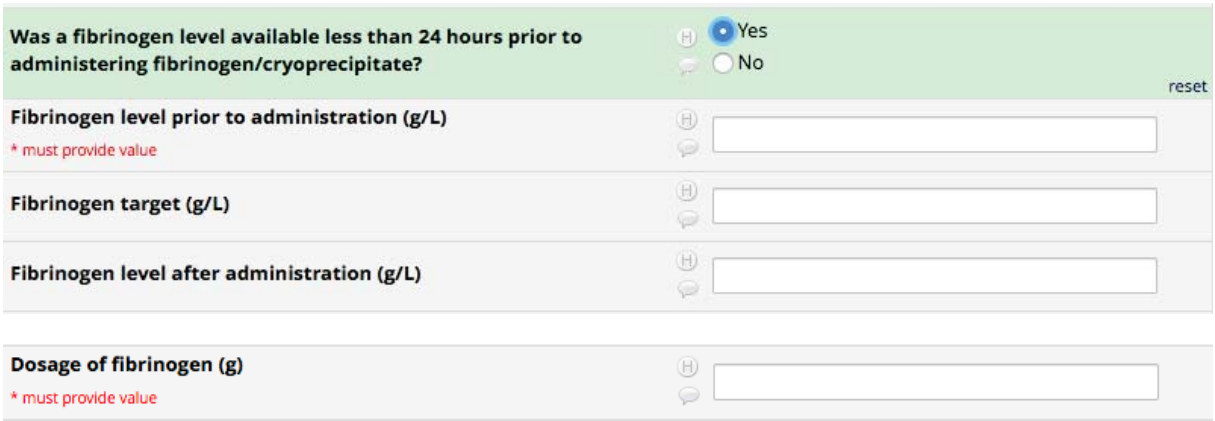
- Cryoprecipitate

Worldwide variance exists for treating low fibrinogen levels with fibrinogen or cryoprecipitate. In the following questions the fibrinogen level prior to and after administration and target level is asked. Also dosage of either fibrinogen or cryoprecipitate needs to be filled in.

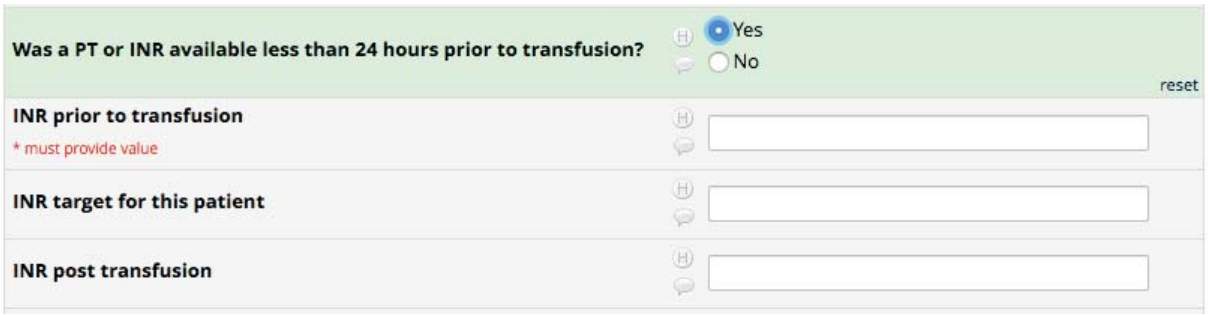


- Fibrinogen

Worldwide variance exists for treating low fibrinogen levels with fibrinogen or cryoprecipitate. In the following questions the fibrinogen level prior to and after administration and target level is asked. Also dosage of either fibrinogen or cryoprecipitate needs to be filled in.



- Prothrombin complex concentrate



Dosage of prothrombin (IE)
* must provide value

- Tranexamic acid

Dosage of tranexamic acid (mg)
* must provide value

- Vitamin K

Dosage of vitamin K (mg)
* must provide value

MASSIVE TRANSFUSION (PROTOCOL)

Was a Hb or a Ht value available less than 24 hours prior to transfusion?	Yes / No (reset)
Hb prior to transfusion (g/dL) * must provide value	
Hb threshold for this patient (g/dL)	
Hb post transfusion (g/dL)	

Number of transfused red blood cell units this transfusion episode * must provide value	

See explanation under TRANSFUSION / RED BLOOD CELL TRANSFUSION

Was a platelet count available less than 24 hours prior to transfusion?	Yes / No (reset)
Platelet count prior to transfusion (/mm^3) * must provide value	
Platelet target for this patient (/mm^3)	
Platelet count post transfusion (/mm^3)	

Number of transfused platelet units this transfusion episode * must provide value	

See explanation under TRANSFUSION / PLATELET TRANSFUSION

Was a PT or INR available less than 24 hours prior to transfusion?	Yes / No (reset)
INR prior to transfusion * must provide value	
INR target for this patient	
INR post transfusion	

Number of transfused plasma units this transfusion episode * must provide value	

See explanation under TRANSFUSION / PLASMA TRANSFUSION

Was an aPTT available less than 24 hours prior to transfusion?	(●) Yes ( ) No reset
aPTT prior to transfusion (sec) * must provide value	
aPTT target for this patient (sec)	
aPTT post transfusion (sec)	

Following factors given (multiple answers possible) * must provide value	☐ None ☐ Apropitin ☐ Cryoprecipitate ☐ Factor VIIa ☐ Factor XIII ☐ Fibrinogen ☐ Novoseven (eptacog alfa) ☐ Prothrombin complex concentrate ☐ Tranexamic acid

DAY 28: PATIENT OUTCOME

Number of days admitted to ICU
* must provide value

The amount of calendar days this patient was admitted at the ICU.

For example:
1) a patient was admitted at the ICU at the 5th or March at 23:55. He passed away at th 6th of March at 00:05. In this case this patient was admitted for 2 days.

Is the patient still alive at the 28th day after ICU admission?

Patient outcome
* must provide value
- (•) Death
- ( ) Alive
- ( ) Unknown

reset

Location of death
* must provide value
- ( ) Died during ICU admittance
- ( ) Died after ICU admittance, inside the hospital
- ( ) Died after ICU admission, outside the hospital

reset

Patient outcome
* must provide value
- ( ) Death
- (•) Alive
- ( ) Unknown

reset

Current location at day 28
* must provide value
- ( ) ICU
- ( ) ICU readmission
- ( ) Discharged from hospital
- ( ) General ward

reset

Patient outcome
* must provide value
- ( ) Death
- ( ) Alive
- (•) Unknown

reset

Location
* must provide value
- ( ) Discharged from ICU, status after discharge unknown
- ( ) Transferred to other ICU, current status unknown
- ( ) Discharged from hospital, status after discharge unknown

reset

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InPUT-study

Study protocol

Version 10

International **P**oint Prevalence Study of Intensive Care **U**nit **T**ransfusion Practices

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

Protocol ID	***<include protocol ID given by sponsor or investigator>***
Short title	InPUT-study
Version	10
Date	14-7-2022
Coordinating investigator/project leader	S.J. Raasveld, MD S. de Bruin, MD, PhD Department of Intensive Care Medicine
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) **Multicenter research:**	A.P.J. Vlaar, MD, PhD Laboratory of Experimental Intensive Care and Anaesthesiology & Department of Intensive Care Medicine & Department of Internal Medicine. Tel. 00-31-20-5669111
Sponsor (in Dutch: verrichter/opdrachtgever)	*Academic Medical Center, Amsterdam, The Netherlands*
Subsidising party	N/A
Independent expert (s)	

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department: **Prof dr. Margreeth.B. Vroom;** **Department of Intensive Care Medicine**		
Coordinating Investigator/Project leaders: **Alexander P.J. Vlaar, MD, PhD**		

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**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)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
GCP	**Good Clinical Practice**
Hb	**Hemoglobin**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICU	**Intensive care unit**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
INR	**International Normalized Ratio**
METC	**Medical Research Ethics Committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie (METC)**
(S)AE	**(Serious) Adverse Event**
Sponsor	**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.**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

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, Australia, Africa 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 threating 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 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 an 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 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.

No informed consent.

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[17,22]. 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[19].

2.5 Sub group analyses

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

- Per blood product: behaviour, reasons and triggers
    - Platelet transfusion in the ICU
    - Practices of plasma transfusion in the ICU
- National transfusion behaviour
- The consistency of transfusion practice in non-bleeding ICU patients; does length of stay effect transfusion policy
- Different sub-groups, including:
    - Septic patients
    - Elderly patients
    - Oncology patients
    - Haematology patients
    - Patients with cardiovascular diseases, acute coronary syndrome & other
    - Patients with traumatic brain injury
    - Patients with ARDS
    - Patients post-cardiothoracic surgery
    - Patients with shock
- Thrombocyte course and thrombocytopenia in the ICU
- Transfusion behaviour between the sexes
- Influence of transfusion on mortality

3. METHODS

3.1 Study parameters/endpoints

3.1.1 Main 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 compared to the haemoglobin levels, platelet count, INR (or PT), fibrinogen stated as threshold for transfusion as well as the *actual* value on which a transfusion is administered.

3.1.2 Secondary parameters/endpoints

Secondary parameters will include:

- Reasons and triggers stated for transfusion;
- Adherence to stated thresholds;
- Mortality and length of stay in the ICU.
- Differences of transfusion practices 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.

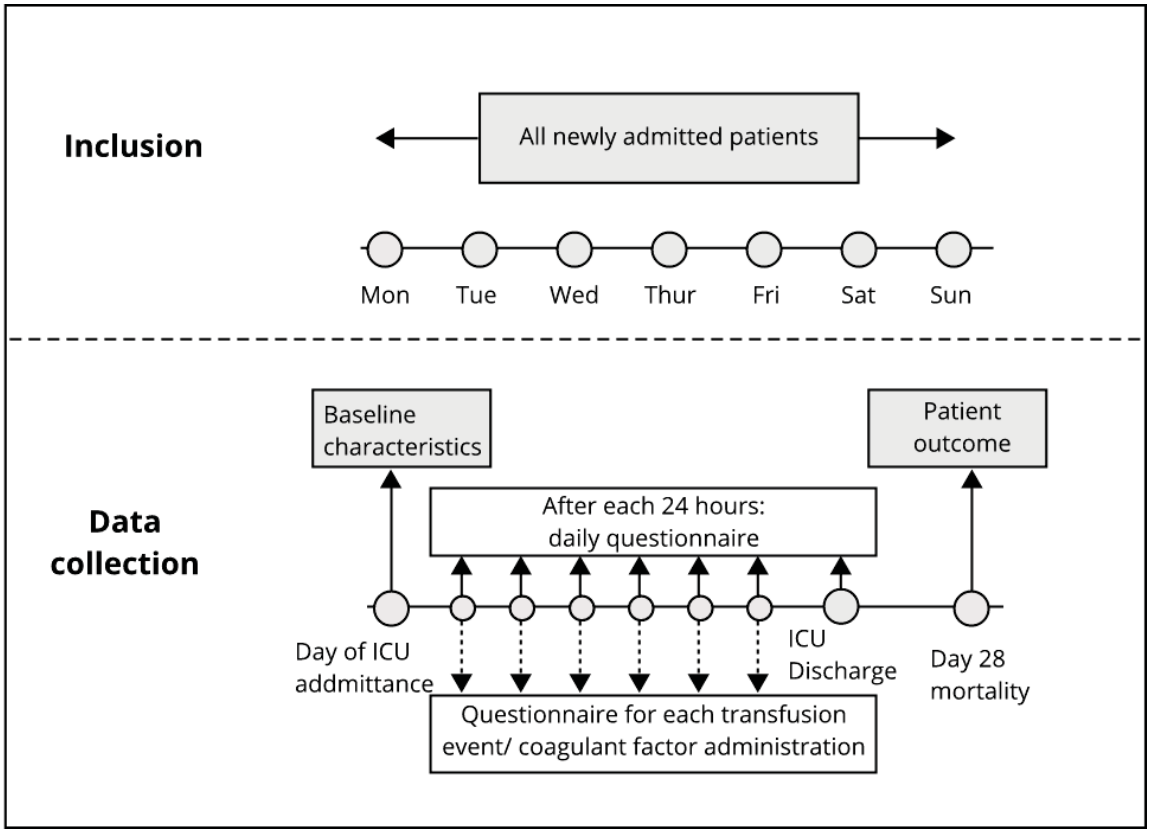

Figure 1. Workflow InPUT study

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
- Renal replacement therapy during that day

Questionnaire per transfusion event:

- General
  - o Active bleeding
  - o Bleeding control
- **Red cell transfusion**
  - o Haemoglobin(Hb)/haematocrit (Ht) level
    - o Hb threshold for this patient

  - Presence of physiological trigger, and which trigger has been used.
  - Transfusion relevant comorbidity
  - Number of units transfused
  - Origin of transfusion product (e.g. allogeneic, autologous, cell salvaged blood)
- **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 transfusion**
  - 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, apropitin, 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
- COVID-19 status

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. Parametric 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 chi-square or Fisher's exact test. To correct for multiplicity, p-value adjustment will applied when appropriate, using for example Bonferroni or Benjamin-Hochberg methods.

To define the actual transfusion behaviour, a mixed-effects model will be created, using transfusion as the dependent variable and the corresponding laboratory value as the predictor variable. Covariates used for case-mix correction will be determined a priori.

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 in the statistical analysis plan (SAP) as further developed for the sub-study.

For all analyses, a p-value <0.05 will be considered to be significant.

5.3 Handling missing data

Different patterns can be found with regard to missing data, including missing-at-random (MAR), missing completely at random (MCAR) and not missing at random (NMAR). Depending of this missingness pattern, different strategies for handling missing data are advised. Most methods assume data is MAR. However, in case of NMAR, methods to handle the missing data points can be most complex.

Therefore, we will evaluate the missing count and pattern using the *naniar* and *visdat* packages. By using these packages, we can identify the combinations of missingness and

intersections of missingness amongst variables. Afterwards, patient data will be excluded when the combination of missing data shows a very high percentage. In addition, certain quality checks will be performed, including the following:

- No. of daily questionnaires available *is equal to* days of ICU admission (with a maximum of 28 days)
- Daily questionnaire: RBC transfused *is equal to* transfusion questionnaire for that day available
- In case of non-transfused: demographics, daily and outcome questionnaire available
- In case of transfused: demographics, daily, transfusion and outcome questionnaire available
- In case of ICU stay >3 days: concomitant dates

Dependent on the further analyses, missing data will be handled accordingly. For example, imputation methods can be applied (as a sensitivity analysis) when working with a model.

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. Institutional review board approval will be obtained by the participating institutions according to local ethical regulations. Informed consent procedures differ between countries, as a result, national regulations will be followed. In case of doubt, written informed consent will be encouraged.

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. Used data as written in the case report form will not contain any identifiable or relatable data. All handling of personal data will comply with the European General Data Protection Regulation act and the '*Reuse of care data for the purpose of research'* standard of the AMC. More details on handling and storage of the data can be found in the Data Protection Impact Analysis and Data Management Plan.

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

7.3.1 Clinical trial registration

The study is registered at the Dutch Clinical Trials Registry, 'The Netherlands National Trial Register (NTR)'. It is registered under trial number NL9049.

7.3.2 UK IRAS

In the UK it is registered as IRAS Project ID 281395.

7.3.3 Publication

We are free to make a publication and have no restrictions made by a sponsor. The results of the study will find their way into (inter–)national scientific journals and guidelines. We will submit analyses to scientific journals in the field of intensive care medicine

8. TIMELINE

April 2018:	Writing study protocol
January-February 2019:	Pilot study in Amsterdam testing feasibility
April 2018-December 2019:	Recruiting Centres
August 2019- Sept 2021:	Obtaining approval from institutional review boards for each country
March 2020	Start data collection
August 2022	Data analysis
December 2022	Writing manuscript

Scheduled inclusion weeks

Inclusion week #	Week number	From (dd-mm-yyyy)	Up to and including (dd-mm-yyyy)	Year
1	10	2-3-2020	8-3-2020	2020
2	16	13-4-2020	19-4-2020	2020
3	22	25-5-2020	31-5-2020	2020
4	30	20-7-2020	26-7-2020	2020
5	37	7-9-2020	13-9-2020	2020
6	43	19-10-2020	25-10-2020	2020
7	49	7-12-2020	13-12-2020	2020
8	3	18-1-2021	24-1-2021	2021
9	10	8-3-2021	14-3-2021	2021
10	15	12-4-2021	18-4-2021	2021
11	21	24-5-2021	30-5-2021	2021
12	26	28-6-2021	4-7-2021	2021
13	31	2-8-2021	8-8-2021	2021
14	38	20-9-2021	26-9-2021	2021
15	43	25-10-2021	31-10-2021	2021
16	48	29-11-2021	05-12-2021	2021

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