



**TEMPLATE RESEARCH PROTOCOL
for non-WMO-applicable research**

19-01-2023, versie 2

Full title of protocol	Prehospital transfusion outcomes in traumatic hemorrhage: a prospective cohort study
Short title or Acronym	PRONTO study
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Sponsor⁴ (in Dutch: verrichter/opdrachtgever)	<i>Erasmus MC</i>
Subsidizing party⁵	<i>Not applicable</i>

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1. *Coordinating investigator: Investigator who bears the responsibility for the coordination of investigators operating in the various centers participating in multicenter research. Not all multicenter research will have a coordinating investigator. There is no requirement to appoint one. A project leader has the responsibility to develop a research protocol and to complete the study within the predefined goals.*
2. *Principal investigator: Investigator who has the overall responsibility to comply and to complete the study within the predefined goals.*
3. *Multicenter research: as an alternative you can also state that these are specified in the list with participating centers including principal investigator. This separate document with version date must be uploaded under category I1.*
4. *Sponsor: The party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or the investigator's employee. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.*
5. *Subsidizing party: A party that provides funding for a study but does not commission it*

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Please note that it is not allowed to remove paragraphs from this template protocol. If a paragraph is not applicable, please mention this in the specific paragraph, preferably with a short motivation.

List of abbreviations and relevant definitions*

CTA	Clinical Trial Agreement
BMI	Body Mass Index
De novo biobank	A new data, human material or imaging collection
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DTA	Data Transfer Agreement
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
eFAST	Extended Focused Assessment with Sonography for Trauma
Exception consent	Form Care for data Template, in Dutch: Formulier uitzondering toestemming
FDP	Freeze Dried Plasma
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation in Dutch: Algemene Verordening Gegevensbescherming
HEMS	Helicopter Emergency Medical Services
HR	Heart rate
IC	Informed Consent
ICU	Intensive Care Unit
IFU	Instruction For Use
IO	Intraosseous
IV	Intravenous
MAP	Mean Arterial Pressure
MMT	Mobiel Medisch Team
MODS	Multiple Organ Dysfunction Syndrome
MOF	Multiple Organ failure
MTA	Material Transfer Agreement
MTP	Massive Transfusion Protocol
MVC	Motor Vehicle Crash

NWTC	Non-WMO Review Committee; in Dutch: Niet WMO Toetsingscommissie
PCC	Prothrombin Complex Concentrate
(p)RBC	(packed) Red Blood Cell
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
(S)AE	(Serious) Adverse Event
SBP	Systolic Blood pressure
SOFA	Sequential Organ Failure Assessment
TBI	Traumatic Brain Injury
TIC	Trauma Induced Coagulopathy
TTE	Transthoracic Echocardiogram
TXA	Tranexamic Acid
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet Algemene Verordening Gegevensbescherming
WMO	Medical Research Involving Human Subjects Act, in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

**Please add any new definitions that are used in the research protocol*

Summary

Rationale

Trauma is a leading cause of death among younger people worldwide, with a large proportion of preventable mortality resulting from severe hemorrhage. Early initiation of transfusion has been shown to reduce mortality, highlighting the importance of timely management in the prehospital setting. Blood components, such as plasma may contribute beneficially to patient management due to their biological properties. Despite theoretical advantages, evidence supporting prehospital transfusion remains inconsistent, leading to uncertainty in guidelines. Additionally prehospital transfusion brings logistical and financial challenges. In the Netherlands the Helicopter Emergency Medical Service (HEMS) supplements standard ambulance care in life-threatening situations. The Dutch HEMS carries 2 units of red blood cells (RBCs), 1g tranexamic acid (TXA) and 2g fibrinogen. Since this year, 2 units of freeze dried plasma (FDP) were added as a transfusion product at two of the four HEMS stations. Studies on prehospital transfusion programs have been conducted in other countries, however such research is lacking within the Dutch HEMS population. Although several recent international studies have evaluated transfusion strategies in trauma patients, important differences in prehospital trauma systems and product availability limit direct extrapolation to the Dutch setting. Resulting in a significant gap in knowledge regarding optimal pre-hospital transfusion strategies and subsequent in-hospital management of hemorrhaging trauma patients in the Netherlands. This study therefore aims to evaluate the HEMS transfusion protocols to identify the association between different transfusion strategies and clinical outcomes.

Objective(s)

The primary objective is to evaluate the impact of the differing transfusion strategies employed across Dutch HEMS bases for trauma patients with (signs of) massive haemorrhage on 24 hour mortality. The secondary aim is to identify and describe prehospital and in-hospital characteristics and clinical outcome measures of trauma patients suffering from severe haemorrhage.

Study type

This study will be a prospective observational cohort study.

Study population

An adult trauma population (>16 years) with (signs of) massive bleeding who were attended to by the HEMS and brought to a level 1 trauma center.

Methods

Directly after arrival of the HEMS team on site, the physician will assess and treat the patient according to standard HEMS guidelines and Advanced Trauma Life Support (ATLS) standards. After a patient is admitted to the emergency department (ED) and the HEMS physician is no longer involved in patient care, the physician will complete routine medical documentation in the HEMS electronic patient record (EPD). When the routine documentation is completed the HEMS physician will also record a limited number of study-specific variables related to prehospital care that are not routinely captured in the HEMS EPD. After inclusion in the castor database the research team will extract all remaining study data on the clinical course and outcomes from the HEMS EPD, the emergency medical service (EMS), the patients hospital medical record and the Dutch National Trauma Registry. Patients will be followed for 30 days or until death, whichever comes first.

Burden and risks

Standard of care will not be influenced by this study. No additional procedures will be performed and patients will not be asked to fill in questionnaires, resulting in very low burdens and risks. The collected clinical outcome data will be anonymized and stored on castor, which meets good clinical practice (GCP) standards.

Recruitment and consent

All participants will be enrolled through an opt-out procedure. All patients who survive the acute phase will receive study information as soon as reasonably possible after admission and will be provided with a 30-day opportunity to object to the use of their data. If a patient opts-out, all their data will be removed from the study database and excluded from analyses. Patients who die before information can reasonably be provided will remain included.

1. Introduction and rationale

Trauma is one of the leading causes of death among younger people (1). According to the World Health Organization (WHO) (2) injuries are responsible for approximately 4,4 million deaths around the world every year. Most preventable deaths following trauma are due to hemorrhage (3) and occur rapidly after injury. Previous research has shown that early initiation of transfusion reduces mortality in hemorrhaging patients (4-6). This highlights the need for timely appropriate management of bleeding patients in the pre-hospital setting.

Uncertainty remains regarding the actual benefit of prehospital transfusion. While early prehospital transfusion appears to be a logical step in achieving hemostatic resuscitation at an early stage, the available evidence is inconsistent. Studies report conflicting results and lack robust data demonstrating a clear survival benefit (7-10). This uncertainty has limited the development of clear recommendations and guidelines on prehospital transfusion (11). Additionally, the use of prehospital blood products poses logistical and financial challenges in a setting with already limited resources.

In the Netherlands the Helicopter Emergency Medical Service (HEMS), also called the 'Mobiel Medisch Team' (MMT) is an addition to the usual ambulance care (12). The Dutch HEMS consists of four bases and is deployed when a patient's health is acutely and severely threatened. The decision to deploy the HEMS can be made by the dispatcher in the emergency control room or by care providers on the scene. Currently, all Dutch HEMS carries 2 units of red blood cells (RBCs), 1g tranexamic acid (TXA) and 2g of fibrinogen. Since this year 2 units of OctaplasLG Lyo freeze dried plasma (FDP) were added as a transfusion product at two HEMS stations. On the HEMS bases equipped with both RBCs and plasma, products are transfused in a 1:1 ratio, in accordance with current literature (13, 14).

Many hospitals and HEMS services have undertaken studies to evaluate prehospital transfusion programs (15-17). However, such studies have not yet been conducted within the Dutch HEMS population. Although several recent international studies have evaluated transfusion strategies in trauma patients (18, 19), important differences in prehospital trauma systems and product availability limit direct extrapolation to the Dutch setting. Resulting in a significant gap in knowledge regarding optimal pre-hospital transfusion strategies and subsequent in-hospital management of hemorrhaging trauma patients in the Netherlands. Therefore, this study proposes to assess prehospital transfusion practices in the Netherlands and identify the association between different transfusion strategies and clinical outcomes.

2. Objective(s)

The primary objective is to evaluate the impact of the differing transfusion strategies employed across Dutch HEMS bases for trauma patients with (signs of) massive hemorrhage on 24 hour mortality.

Secondary Objective(s) are:

1. Identify and describe prehospital and in-hospital characteristics of trauma patients suffering from severe hemorrhage.
2. Identify and describe short- and long-term clinical outcomes.
3. Determine whether specific patient characteristics can predict a greater benefit from prehospital transfusion.

3. Study type

3.1. Study type

☐ Retrospective

- ☒ Prospective
- ☐ Combination Retrospective/Prospective

3.2. Single center / Multicenter

- ☐ Single center
- ☒ Multicenter

3.3 Check all the applicable boxes

- ☒ Medical records (re-use of data from healthcare, including AI)
- ☐ Case report
- ☐ Re-use data from research
- ☐ Evaluations of quality of healthcare (retrospective)
- ☐ Research with additional use of residual material from regular healthcare
- ☐ Research with re-use of human material from research or existing biobank
- ☐ De novo biobank
- ☐ Phase IV research
- ☒ Healthcare evaluation research (prospective)
- ☐ Research with medical devices
- ☐ Research with In Vitro Diagnostic Tests
- ☐ Other research, describe

4. Study population

4.1. Study population

- ☐ Adults (16 years and older)
- ☐ Minors (younger than 16 years)
- ☒ Incapacitated adults (16 years and older)
- ☐ Incapacitated minors (younger than 16 years)

4.2. Population (base)

Adult (>16 years) trauma patients with (signs of) massive bleeding who are attended to by the HEMS and brought to a level 1 trauma center and/or received prehospital transfusion products. Patients will be assessed for eligibility to enter the trial according to the criteria set out below. If patients are eligible for inclusion, after initial screening they will be included through an opt out procedure. Patients are considered eligible for inclusion if they fulfil all the inclusion criteria and none of the exclusion criteria.

4.3. Inclusion criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

1. Adult (age ≥ 16 years)
2. Patients who received prehospital blood products from the HEMS
3. Patient has suffered traumatic injuries
4. Patient is transported to a level 1 trauma center

4.4. Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

1. Physician in prehospital setting decides injuries are incompatible with life before treatment started
2. Transfer from other hospital

4.5. Sample size calculation.

To assess the HEMS transfusion protocols regression analyses will be used. At least 10 observations per variable are needed for a well performed regression analysis. The HEMS Rotterdam was involved in the treatment of 8,962 adult trauma patients during a period from January 1, 2015 to December 31, 2023 (20). Prehospital blood has been part of the standard of care since 2017 on the HEMS. Following its implementation, prehospital blood products were administered to 340 patients up to December 31, 2023 (20). Resulting in an estimate of 50 patients per year receiving prehospital transfusion. The Amsterdam HEMS has a similar amount of transfusion per year. Nijmegen and Groningen HEMS have a lower number of transfusions per year, with roughly 50 transfusions combined between the two bases. This results in a total of 150 patients transfused by HEMS services in the Netherlands each year. We will include all trauma patients who received prehospital transfusion products over a period of 5 years resulting in an estimated sample size of 750 patients. Based on previous literature, we expect approximately 40% of the included patients to experience the primary outcome, resulting in approximately 300

outcome events. Assuming a minimum of 10 events per variable, regression analyses can therefore be reliably be performed with up to 30 variables.

5. Methods

5.1. Research methods

Directly after arrival of the HEMS team on scene, the physician will assess and treat the patient according to standard HEMS guidelines and Advanced Trauma Life Support (ATLS) standards. After life threatening airway and breathing problems are ruled out or resolved, a patient will be assessed for traumatic hemorrhage. External bleeding will be controlled by direct compression or tourniquets and a large bore intravenous (IV) access will be obtained. If a patient is suspected of massive hemorrhage transfusion with packed red blood cells (pRBC's) and (if available) FDP will be initiated, according to the HEMS massive transfusion protocol. Additionally, 1 gram of TXA and 2 grams of fibrinogen will be administered. Once a patient has arrived at a level 1 trauma center local protocols will be followed.

If a patient is suspected of massive hemorrhage the HEMS physician will treat the patient according to standard clinical care. After a patient is admitted to the emergency department (ED) and the HEMS physician is no longer involved in patient care, the physician will complete routine medical documentation in the HEMS electronic patient record (EPD). A limited number of study-specific variables related to prehospital care that are not routinely captured in the HEMS EPD will be recorded in castor by the HEMS physician. After inclusion in the castor database the research team will extract all remaining study data on the clinical course and outcomes from the HEMS EPD, the emergency medical service (EMS), the patients hospital medical record and the Dutch National Trauma Registry. Patients will be followed for 30 days or death whichever comes first.

This multicenter study will initially use data collected exclusively within the Rotterdam HEMS and Erasmus MC. Additional participating hospitals will be included at a later stage. Once these centers join, clinical trial site agreements (CTSA) will be arranged with each participating site.

5.2. Standard clinical care versus extra for research

The standard clinical care will not be affected in this study.

5.3. Burden and risks

The burden and the risks are very low in this study. Standard of care will not be influenced by this study. No additional procedures will be performed. Patients will not be asked to fill in questionnaires or participate actively in the research. The clinical outcome data will be anonymized and stored on castor. The intended study population are participants who have been affected by severe injuries that result in uncontrolled bleeding. Patients that are eligible for inclusion in this study will be incapacitated at the time of screening for this study for multiple reasons including the circumstances of the traumatic event, the nature of their injuries, having severe pain, being under anesthesia, having reduces consciousness and/or the use of strong analgesia. Given that severe traumatic injuries cannot be predicted or anticipated, there is no possibility to identify individuals before the event. Consequently, screening cannot take place prior to the trauma, which makes it necessary to include subjects who are incapacitated.

5.4. Medical device(s) / In vitro diagnostic tests

Not applicable

6. Incidental findings

6.1. Chance of incidental findings

Is there a chance of incidental findings?

☐ Yes

☒ No

6.2. Procedures

Not applicable

7. Statistical analysis

7.1 Main study parameters/endpoints

The primary study endpoint is all cause mortality at 24-hours.

7.2 Secondary study parameters/endpoints

- 1) Total number and ratio of blood products administered in the prehospital setting
 - Mean or median number of products transfused in the prehospital setting
 - Mean or median ratio of RBC's to plasma administered
 - Number of patients and percentage who were transfused in a 1:1 ratio
- 2) Other products administered in the prehospital setting
 - Hemostatic agents (TXA, calcium and fibrinogen)
 - Mean / median number administered
 - Number of patients and percentage that received a certain hemostatic agent
 - Medications
 - Mean / median number administered
 - Number of patients and percentage that received a certain medication
 - Crystalloids
 - Mean / median number transfused
- 3) Prehospital interventions (i.e. intubation, cricothyrotomy, resuscitative endovascular balloon occlusion of the aorta (REBOA), tourniquet use, extracorporeal membrane oxygenation (ECMO), thoracic tube, thoracotomy, perimortem sectio, etc.)
- 4) Vital signs at ED presentation
 - Blood pressure (systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP))
 - Heart rate (HR)
 - Body temperature
 - Oxygen saturation
- 5) Glasgow coma scale (GCS) at ED presentation
- 6) Blood gas results in the ED and in the first 24h after admission
- 7) Lab results from the prehospital setting showing coagulation parameters and markers for inflammation in the ED, 1h after admission, 6h after admission and first 24h after admission
- 8) Extended focused assessment with sonography in trauma (eFAST), Thorax ultrasound and trans thoracic echocardiogram (TTE) results in the ED.
- 9) Number and ratio of blood products administered in the ED
 - Mean or median number of blood products transfused in the ED
 - Mean or median ratio of RBCs to plasma to thrombocytes administered
 - Number of patients and percentage who were transfused in a 1:1:1 ratio in the ED
- 10) Need for massive transfusion at the ED and in the first 24 hours

- Massive transfusion is defined as >4 units of blood products in 3 hours
- Number of patients and percentage that needed massive transfusion
- 11) Other products administered in the ED
 - Hemostatic agents (TXA, Ca, fibrinogen and prothrombin complex concentrate (PCC))
 - Mean / median number administered
 - Number of patients and percentage that received a certain hemostatic agent
 - Medications
 - Mean / median number administered
 - Number of patients and percentage that received a certain medication
 - Crystalloids
 - Mean / median volume transfused
- 12) Interventions performed in the ED
 - (i.e. intubation, cricothyrotomy, REBOA, tourniquet use, ECMO, thoracic tube, thoracotomy, perimortem sectio etc)
- 13) Ratio of blood products in the first hour, 6 hours and 24 hours
 - Mean or median ratio of RBC's to plasma to thrombocytes administered
 - Number of patients and percentage who were transfused in a 1:1:1 ratio
- 14) Interventions in the first 24 hours
 - Number of operations and intervention radiology interventions related to the injury
- 15) Mortality
 - Prehospital
 - 1h
 - 6h
 - 30 days
 - Cause of death
- 16) Length of stay
 - Days in hospital
 - Days in the intensive care unit (ICU)
- 17) Multiple organ dysfunction syndrome
 - Sequential Organ Failure Assessment (SOFA) score ≥ 3 in ≥ 2 organ systems, yielding a minimum SOFA score of 6 -> MODS
- 18) Multiple organ failure
 - Number of organ failure free days (number of days free of advanced cardiovascular, respiratory and renal support)
- 19) Coagulopathy
 - Number and percentage of patients with Disseminated intravascular coagulation (DIC), defined as a Japanese Association for Acute Medicine (JAAM) DIC score of ≥ 4
 - Number and percentage of patients with TIC, defined as INR >1.5 OR fibrinogen <1.5 g/l OR PT >18 s OR FIBTEM A10 <10 mm, prehospital, at ED presentation and 6h after trauma.
- 20) Thrombosis
 - Number of patients and percentage with:
 - Pulmonary embolism
 - Deep venous thrombosis
- 21) Adverse events related to transfusion
 - Number of patients and percentage with:
 - TRALI
 - TACO
 - Hemolytic transfusion reaction
 - Allergic reaction

7.3 Other study parameters

- 1) Patient demographics
 - Age (calculated from date of birth to date of trauma)
 - Sex (male or female)
 - Weight
 - Height
 - Body mass index (BMI)
 - Anticoagulant use
- 2) Trauma and injury details
 - Mechanism of injury
 - Blunt
 - Motor vehicle crash (MVC)
 - Fall
 - Other
 - Penetrating
 - Stabbing
 - Gunshot
 - Other
 - Prehospital eFAST and TTE results
 - Injury severity score (ISS)
 - Prehospital vital signs at arrival and departure
 - Oxygen saturation
 - Heart rate
 - SBP
 - DBP
 - MAP
 - Temperature
 - GCS
 - GCS-score at arrival and departure
 - Traumatic brain injury (TBI)
- 3) Prehospital services information
 - Time ambulance was dispatched
 - Time HEMS was dispatched
 - Ambulance time of arrival

- HEMS time of arrival
- Ambulance arrival >15 minutes before HEMS
- Mode of transport
 - Ambulance or helicopter
- Hospital arrival time

Analysis

Data will be analyzed using R software and R-studio (R Foundation for statistical Computing, Vienna, Austria). Normality of continuous data will be visually assessed and tested with the Shapiro Wilk test. A two sided p-value <0.05 will be used as a threshold for statistical significance in all statistical tests.

Variables with more than 10% missing values will be considered for multiple imputation following the predictive mean matching method, using ten imputations. Imputation will only be performed if it can be assumed that values were missing at random.

Patients will be divided into groups related to the transfusion strategy. Continuous data will be reported as means with a standard deviation (SD). For non-parametric continuous data median and inter quartile range (IQR) will be used. For categorical data, numbers and frequencies will be reported per subgroup. Descriptive analyses will be performed for all baseline characteristics and clinical outcome measures. Differences between groups will be assessed with the following analyses: for continuous parametric data a T-test will be used. If continuous data is skewed a Wilcoxon rank sum test will be used. Categorical data will be analyzed with a chi squared or Fishers exact test.

The primary analysis investigating the effect of different transfusion strategies (RBCs + plasma vs RBCs only) on 24-hour all-cause mortality will be conducted using a log-binomial regression model.

24-hour mortality will also be assessed using a multivariable logistic regression model and a Kaplan Meier survival curve. Confounders for all analyses will be selected based on variables with a statistically significant ($p < 0.10$) or clinically relevant differences in baseline characteristics.

Secondary outcomes will be assessed as well. All-cause prehospital mortality, 1 hour mortality and 6 hour mortality will be assessed with a logistic regression and 30 day mortality will be assessed with a cox proportional hazard model. Given the possibility that the proportional hazards assumption may not hold due to the expected time dependent effect of transfusion strategy, this assumption will be formally assessed using Schoenfeld residuals and visual inspection of $\log(-\log(\text{survival}))$ vs $\log(\text{time})$ plots for each covariate. If the assumption is violated an adjusted restricted mean survival time (RMST) analysis up to 30 days will be performed additionally. If the proportional hazards assumption is not violated, the cox regression will be performed as planned. To assess changes from baseline characteristics, blood gas results and lab values overtime a mixed model for repeated measures will be used. A logistic regression will be performed to assess the amount of patients transfused in a 1:1:1 ratio in the ED, the amount of patients with TIC in the ED and at six hours and the amount of patients transfused with the need for massive transfusion in the ED and at the first 24 hours. Length of stay in the ICU and in-hospital will be assessed using a negative binomial regression analysis.

8. Ethical considerations

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 2024), Gedragscode Gezondheidsonderzoek 2022 and in accordance with other guidelines, regulations and Acts (if applicable, please specify).

8.2 Informed consent

Will the subjects be asked for informed consent?

☐ Yes (*Upload Participant Information Letter and Informed Consent*)

☐ No, consent already given in previous study (*Upload Participant Information Letter and Informed Consent previous study*)

☐ No, this research will be performed under the exception consent (*Upload form Care for data Template, in Dutch: Formulier uitzondering toestemming*)

☒ Other (e.g. partly, indirectly) *Opt-out procedure (Patient Information Letter and Opt-out form will be uploaded as an amendment)*

Recruitment and informed consent procedures

Due to the emergency nature of this trial participants will be enrolled in the study through an opt-out providing participants with a chance to refuse inclusion in the study at a later time. The intended study population consists of patients who have been affected by severe injuries that result in uncontrolled bleeding. Most patients will be incapacitated at the time of screening for this study for multiple reasons, including the circumstances of the traumatic event, the nature of their injuries, having severe pain, being under anesthesia, having reduced consciousness and/or the use of strong analgesia. Additionally, traumatic injury can't be predicted or foreseen, making it impossible to seek consent in advance. Participants will therefore be incapable of giving informed consent prior to enrollment in the study. In the rare event that a participant retains the capacity to give consent in the prehospital setting, their clinical condition will still require immediate resuscitation. It would be inappropriate to delay life-saving treatment and transport in order to seek informed consent. For the same reason it would be clinically unjustifiable to delay treatment until full informed consent can be obtained by proxy

An opt-out procedure was chosen, because requiring informed consent after recovery could introduce substantial selection bias. Patients with the most severe injuries are more likely to remain critically ill for prolonged periods. It is often uncertain whether or when they will regain the capacity to provide informed consent. Furthermore, legal representatives are often confronted with major emotional distress during this period and may not be in a position to adequately consider research participation. Being approached about research during this period may be perceived as an additional burden. As a result, a proxy may be less likely to engage in a consent procedure, regardless of the minimal burden associated with this study. Requiring active informed consent would therefore be expected to result in systematic underrepresentation of the most severely injured patients, particularly those with prolonged critical illness. Therefore, the study population would no longer reflect the population of patients with severe traumatic hemorrhage, possibly compromising the validity, generalizability and clinical relevance of the study findings. To balance scientific validity with respect for a patients autonomy, surviving patients will be informed about study participation as possible and provided with a 30-day opportunity to opt-out from participating in the study.

Patients who survive the acute phase will receive study information as soon as reasonably possible after admission and will be offered the opportunity to object to the use of their data within 30 days. The information letter will explain the purpose of the study, the type data collected and the opt-out procedure. If after 30 days no response was received, the patient will stay included in the study. Data from participants who opt out will be removed from the study database and will not be included in the analyses.

In the event that a participant dies during the study, there may have been no opportunity for contact with the research team. In this instance, we recognize that approaching a proxy to ask their opinion is likely to be distressing and without benefit. It is unethical to burden grieving relatives with a decision that had no impact on already performed treatment and only pertains the use of already collected and coded data. The data will be coded so use of data has no implications for the patient or legal representatives. Therefore, we will not approach a proxy to seek their opinion when a participant dies.

8.3 Exception consent

Not applicable

9. Handling and storage of data / images / sound recordings / photos / film recordings

9.1 Data / images / sound recordings / photos / film recordings

For research purposes only, clinical parameters and outcome data will be extracted from the medical records from the HEMS and level 1 trauma centers. Data will be stored using Castor, which meets Good Clinical Practice (GCP) standards. Research data that can be traced to individual persons can only be viewed by authorized personnel. Members of the research team and members of the health care inspection are authorized personnel.

9.2 Privacy protection

Research data will be stored under a code number that relates to individual participants. This code consists of the study acronym and four numbers for patient ID. A subject identification code list will be used and saved in a separate file. Only the code number will be used for study documentation, annual progress reports, and research publications. The principal investigator (PI) and research assistant are the only people with the information linking individual participants to study code numbers. This data will be stored during the investigation and will be disposed of 10 years after completion of the study. The pseudonymized database will be stored on castor, for the duration of the study. Only researchers involved in the study will be granted access to the castor. The handling of personal data will be in compliance with the EU General Data Protection Regulation (in Dutch: 'Algemene Verordening Gegevensbescherming (AVG)).

9.3 Handling and storage of data

Once the data is obtained from the medical records, the principle investigator will remove all identifiable characteristics and every case will be given a subject code, that consists of the study acronym and three numbers for patient ID. Researchers involved in the project will be granted access to the database in castor. In line with Erasmus MC guidelines, data will be kept 10 years after it is collected.

9.4 Handling and storage of images / sound recordings / photos / film recordings

No images / sound recordings / photos/ film recordings will be used in this study.

9.5 Approval of access to data / images / sound recordings / photos / film recordings

Access to the coded data is granted by the PI.

10. Handling and storage of human material

10.1 Human material

No human material is used in this study

10.2 Check all the boxes which are applicable to the human material origin:

☐ Residual material from regular healthcare

☐ Research (material acquired from a previous study).

Add the reference of the study i.e., MEC-number Erasmus MC.

☐ Re-use of human material from existing biobank

Describe whether the human material originates from research into the same disease.

☐ Other, *please specify*

Not applicable

10.3 Handling and storage of human material

☐ Anonymous, i.e. the material can never be traced back to an individual subject

☐ Pseudonymized/Coded

☐ Identifiable

Not applicable

10.4 Biobank

Not applicable

10.5 Approval of access to human material

Not applicable

11. Exchange, sharing or transfer of data and/or human material and/or images

This multicenter study will initially use data collected exclusively within the Rotterdam HEMS and Erasmus MC. Additional participating hospitals will be included at a later stage. Once these centers join, clinical trial site agreements (CTSA) will be arranged with each participating site.

12. Amendments

Amendments are changes made to the research after a favorable opinion by the NWTC has been given.

All amendments must be submitted to the NWTC that gave the favorable opinion.

Substantial amendments must be approved by the Niet WMO Toetsingscommissie before they can be implemented.

13. End of study report

Within one year after the end of the study a final study report will be submitted with the results of the study, including any publications/abstracts of the study.

14. Publication

Do you have the intention to submit the study results in a manuscript for publication in a journal:

☒ Yes

☐ No, *please motivate*

15. References

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16. Attachments

- ☐ Participant information letter and Informed consent document
- ☐ Care for data Template – Formulier uitzondering toestemming
- ☐ Questionnaires
- ☐ Data Management Plan
- ☐ Data Transfer Agreement
- ☐ Material Transfer Agreement
- ☐ Clinical Trial (Site) Agreement
- ☐ Other, *please describe*