UNIL | Université de Lausanne
Faculty of Biology and Medicine

DETAILED STATISTICAL ANALYSIS PLAN (SAP)

1. Administrative information

1.1 Title, registration, versions and revisions

Full Study Title	Prediction of massive transfusion in trauma patients in prehospital and in-hospital. Data from Swiss trauma System: Swiss trauma Registry (STR)
Acronym	Massive Transfusion Prediction Study (MTP study)
Clinicaltrial.gov number	Swiss Trauma Registry (STR): NCT03526029 *MTP study: pending approval*
Study Protocol Version	V 1
SAP version	1.0 (11 September 2020)
SAP Revision History	None
SAP Revision Justification	-
SAP revision timing	-

1.2 Roles and Responsibilities

Author	Alan Costa[1]
Statistician	Doctor François-Xavier Ageron[1]
Principal investigator	Alan Costa[1]
Contributors and Roles	Doctor François-Xavier Ageron[1]: Chief Investigator, revised the SAP Professor Pierre-Nicolas Carron[1]: Chief investigator
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1.3 Signatures

The investigators, the undersigned, certify that the investigators read this SAP and approve it as adequate in scope of the main- analyses of the MTP Study.

1.3.1. Author and Principal investigator

Name: Alan Costa

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Date:

1.3.2. Statistician and Chief investigator

Name: Doctor François-Xavier Ageron

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Date:

1.3.3. Chief Investigator

Name: Professor Pierre-Nicolas Carron

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Date:

1.4 Abbreviations and definitions

SAP: Statistical Analysis Plan

MT: Massive Transfusion

AIS: Abbreviated Injured Scale

ABC: Assessment of Blood Consumption

RBC: Red Blood Cell

FAST: Focus Assessment with Sonography Trauma

BATT: Bleeding Audit and Triage Trauma Score.

TASH : Trauma-Associated Severe Haemorrhage

STR: Swiss Trauma Registry

ISS: Injury Severity Score

SBP: Systolic Blood Pressure

GCS: Glasgow Coma Scale

FFP: Fresh Frozen Plasma

TBI: traumatic brain Injury

CPR: Cardiopulmonary reanimation

2. Introduction

2.1 Background and rationale

Since the 2000s, many prognostic scores were developed to predict traumatic haemorrhage. Most of these studies were retrospectives based on registers. Due to missing data on death due to bleeding, these studies chose to predict the massive transfusion risk as a surrogate of haemorrhagic death. These scores include clinical parameters (vital signs), laboratory values (Haemoglobin, lactate, Base excess) and/or imaging (CT or ultrasound) values. The scores showing best performance are the Trauma Associated Severe Haemorrhage (TASH) score, developed and validated on the German register (DGU-Register) (1, 2) and the ABC score developed and validated in the United States of America (3, 4). The scores with variables are described on Figure 1,2.

However, the majority of these scores cannot be applied at the trauma scene due to the unavailability of laboratory and imaging values. Therefore, their clinical utility remains unclear. To overcome the need for diagnostic tests, authors have developed and recently validated a clinical prognostic score in identifying trauma patients with, or at risk of, significant haemorrhage based on predicted probabilities of death due to bleeding: BATT score (5). This score was developed from an international cohort using data from 271 Trauma Centres in 41 countries on 5 continents and uses first clinical parameters at initial assessment. The BATT score predicts death due to bleeding and has been validated on a large population in England and Wales. It could also predict massive transfusion, as a surrogate of haemorrhagic death, earlier at the trauma scene. Its feasibility and external validation would make its clinical utility superior to other scores while identifying a greater number of patients requiring early management.

Our study is an external validation of pre-existing prognostic scores of traumatic haemorrhages (TASH[1,2], ABC[3,4] and BATT[5] score) at different times of care (Scene of Injury, admission at the trauma room) in order to assess their overall performance, discrimination and calibration in the prediction of massive transfusion, and haemorrhagic death. The objective of the study is to assess a comparison of score performances (Overall performance, discrimination and calibration).

3. Study Methods

3.1 Study Design

The MTP STUDY is a retrospective, observational, non-interventional study based on a multicentric, anonymised Register. The Study is conducted by the emergency department of the University Hospital (CHUV) in Lausanne, Switzerland. The study design is observational, and no intervention is applied as part of the study protocol.

The SAP of this study will be registered at www.clinicaltrials.gov.

3.2 Sample Size and Power consideration

As his study is retrospective, the sample size is fixed. The number of participants will depend on the STR Database. The investigators anticipate using the data of 10'000 participants included in the Swiss Trauma Registry from 1st January 2015 to 31st December 2019. A post-hoc power calculation will be performed.

3.3 Timing of Final analysis

This statistical plan will be added to the study protocol at www.clinicaltrials.gov, after receiving the STR approval. It will be added before receiving the dataset and before any analyses have been conducted.
After receiving the dataset, the investigators will check for data consistency. Once the database has been checked, statistical analysis will be performed (October 2020)

3.4 Ethical Approval

As is mandatory in Swiss law (KVG), STR is authorised **by the Human Research Act (HRA)** as a quality registry for the Highly Specialised Medicine (HSM). Due to the retrospective aspect of our observational study based on an anonymized registry (identity, date of birth, trauma scene and hospital location unknown) and according to the swiss law by the HRA (Art. 2), the investigators don't need a protocol submission to an ethics committee.

4. Study Population

4.1 Screening Data

The investigators will use data from the Swiss Trauma Registry (STR)[6], which represents the Swiss trauma system, serving the country's 8.6 million inhabitants. The STR collect data on patients with major trauma who have been admitted to a level I Swiss trauma centre (Centre Hospitalier Universitaire Vaudois, Hôpitaux universitaire Genevois, Inselspital Bern, Universitätsspital Basel, Universitätsspital Zürich, Kantonsspital St. Gallen, Luzerner Kantonsspital, Kantonsspital Aarau, Kantonsspital Graubünden, Kantonsspital Winterthur, EOC – Ospedale Regionale di Lugano, Gesundheitsnetwerk Wallis – Standort Sion). Major trauma has been defined according to the inclusion criteria of the STR.

4.2 Eligibility

All trauma patients included in the STR between 01.01.2015 and 31.12.2019 have been recorded according to these inclusion criteria of the STR[6]:

4.2.1. Inclusion criteria

- Age > 16 years old
- ISS ≥ 16 and/or AIS head ≥ 3

4.2.2. Exclusion criteria

- Age < 16 years old
- ISS < 16 and/or AIS head < 3
- Isolated Burns (including electric shock) or if the burn is clearly the primary injury
- Patients arriving at the trauma room without signs of life and no diagnostic/therapeutic measures have been initiated for them
- Choking or Hanging patient without any other injury
- Drowning patients

4.3 Baseline patient characteristics

4.3.1 Collected baseline patient characteristics

The observational study is designed to record a set of demographical data, clinical examination in prehospital or in-hospital setting, in-hospital biochemical values and imaging variables for each included patient. The investigators will extract the data from the Swiss trauma registry (STR). The investigators plan to extract the biological parameters from the register at the trauma room stage. The clinical examinations will be the first measures at the pre and in-hospital stage. **Table 1** provides an overview of all variables requested from the registry before receiving the dataset.

4.3.2 Descriptive summary of baseline patient characteristics

The investigators will list general patient characteristics in a baseline characteristics table. Data will be presented as mean with standard deviation (SD) when normally distributed or as median with interquartile range in case of skewed data. Dichotomous and categorical data will be presented in proportions. **Table 2** provides a summary of potential baseline characteristics.

4.4 Assumed confounding covariate

The majority of the requested variables from the STR are inevitably correlated, as most relate to the haemodynamic status of the patient and the trauma severity. The values of the variables can be confounded by unmeasured factors, such as environmental, genetic or psychological influences. Therefore, the investigators provide an example of possible confounding variables:

- Clinical examinations in prehospital settings (i.e. heart rate, systolic blood pressure, respiratory rate, Glasgow Coma scale) are assumed to be confounded by:
    - Quality of the measurements, stress, pain and anxiety. These confounding covariates should be minor for the statistical analysis.
- Clinical examinations at hospital admission (i.e. vitals signs) are assumed to be confounded by:

  - Quality of the measurements, administration of inotropes and/or vasopressors during transport, administration of propofol (negative inotropic effect), induced comas and the need for mechanical ventilation.
- Because some patients will not survive long enough to receive 10 red blood cell units, massive transfusion is subject to misclassification. To correct this misclassification, the investigators add in the massive transfusion definition the use of ≥ 3 RBC administered in the first hour (if the variable is available in the registry).
- The trauma-induced coagulopathy as secondary outcome is assumed to be confounded by anticoagulant treatments. To counteract the confounding covariate, the investigators will include the fibrinogen < 1.5 g/L in the definition of trauma-induced coagulopathy. The investigators will also define a subgroup of patients with anticoagulant treatment or not.

The investigators acknowledge that there will be residual confounding in our dataset due to the presence of unmeasured confounding, some of which is listed above. However, the actual measured variables reflect daily practice and so are assumed to reflect similar confounding in daily assessments.

5. Analysis

5.1 Outcome definitions

6.1.1 Primary outcome

The primary outcome is the presence of massive transfusion (MT) in Swiss trauma patients, defined by a transfusion equal to or greater than 10 Red blood cell (RBC) in the first 24 hours or ≥ 3 RBC in the first hour if available in the Swiss Trauma Registry.

6.2.2 Secondary outcome

Secondary outcomes are death due to bleeding if available in the registry, early death (< 24 hours) and coagulopathy at hospital admission defined by an INR > 1.2 or TP < 70% or Fibrinogen ≤ 1.5 g/L (each other will be used for sensibility analysis) [7,8,9].

5.2. Analysis methods

5.2.1. Efficacy analyses of primary outcome

First, the investigators will assess the accuracy (overall performance), discrimination and calibration of ABC, TASH and BATT score for the prediction of massive transfusion in trauma patients at the trauma scene and at the hospital admission.

5.2.2. Accuracy

The accuracy will be assessed using the Brier score:

$$\text{Brier Score} = \frac{1}{N}\sum_{i=1}^{n}(Y - p)^2$$

Where Y is the observed outcome and p is the prediction of the model

The Brier score depends on the prevalence of the outcome, the investigators will also calculate the scaled Brier score to account for the baseline risk of Massive transfusion:

$$\text{Scaled Brier score} = \frac{1-Brier}{Brier\ max}$$

The scaled Brier score ranges from 0% to 100% and indicates the degree of error in prediction. A scaled Brier score of 0% shows perfect accuracy.

5.2.3. Discrimination

Discrimination is the ability of the score to correctly identify patients with the outcome. The investigators will estimate the sensitivity, specificity, positive and negative likelihood ratio for the defined threshold of each score (ABC, TASH, BATT).

The likelihood ratio is the likelihood of a positive score in a patient with the outcome compared to the likelihood of a positive score in a patient without the outcome. The positive likelihood ratio is the ratio of sensitivity to 1-specificity. The negative likelihood ratio is the ratio of 1-sensitivity to specificity. A positive likelihood ratio of 10 or above will result in a large increase in the probability of the outcome. A negative likelihood ratio of 0.1 or less will result in a large decrease in the probability of the outcome.

The investigators will plot the Receiving Operating Characteristic (ROC) curve which is the sensitivity (true positives) on 1-specificity (false positives) for each defined threshold of each

score. An ideal score will reach the upper left corner (all true positive with no false positive). The investigators will estimate the area under the ROC curve (AUROC) that corresponds to the concordance statistic (C-Statistic) for binary outcome. A C-statistic of 1.0 shows perfect discrimination ability.

5.2.4. Calibration

Calibration is the agreement between observed and predicted outcomes. The investigators will mostly estimate calibration as the difference between the mean predicted and observed probabilities and the ratio of the predicted and observed number of events (P/O). The investigators will plot the observed and predicted probabilities of massive transfusion by decile of the score and with local regression based on LOESS algorithm. The investigators will estimate the calibration intercept and slope of the calibration plot as a measure of spread between predicted and observed outcome. Ideally, the intercept would be zero indicating that the predictions are neither systematically too low or too high and the slope would be 1.

Unfortunately, the investigators cannot estimate the calibration of the BATT score, because of its different outcome (death due to bleeding and not the massive transfusion as the TASH and ABC score). For the BATT, calibration will be assessed with the outcome of death due to bleeding or early death.

5.2.1.1 Efficacy analyses of secondary outcome

The investigators will perform the same analysis for secondary outcomes as the primary outcome.

5.2 Missing Data

Due to the retrospective aspect of the study based on a multicentric registry, the investigators expect to have some missing data for some prehospital and in-hospital predictors.

5.2.1. Imputation method

To estimate baseline risk for the full dataset, the investigators will replace missing predictors using multiple imputation by chained equations on sex, age, systolic blood pressure, respiratory rate, heart rate, Glasgow coma scale, Haemoglobin, base excess, type of injury (penetrating/blunt) Instable pelvis fracture and open/dislocated femur fracture with 20 imputed dataset. All analysis and results will be present in two subgroups: missing data imputed and missing data excluded.

5.2.2. Early deaths and early deaths with haemorrhage as a proxy for death due to bleeding

Because the investigators don't know if the Swiss Trauma Registry record the cause of death, the investigators expect some missing data about death due to bleeding as a secondary outcome. In case of missing data on secondary outcomes, the investigators will use early deaths and early deaths with evidence of haemorrhage as a proxy for death due to bleeding. Specifically, the investigators will included deaths from all causes within 12 hours of injury (excluding massive destruction of skull or brain; asphyxia, drowning and hanging are already excluded from the STR) and deaths between 12 to 24 hours with evidence of bleeding (Activation of massive transfusion protocol or blood within 6 hours or an abbreviated injury scale (AIS) diagnosis associated with haemorrhage: Blood loss >20%, Aorta [OR] Vena Cava [OR]carotid [OR]femoral [OR]Major arteries [OR]veins AND laceration, - Spleen [OR]liver [OR] Kidney [OR] Myocardium [AND] major laceration, major haemothorax, retroperitoneum haemorrhage).

5.3 Subgroup analyses

If the sample size permits, the investigators will conduct subgroup analysis in different subpopulations for the primary and secondary outcomes. The investigators will create the following subgroups in our MTP study:

- Subgroup 1: subdivide the population into two groups: with or without isolated severe traumatic brain Injury (TBI) with AIS HEAD ≥ 3 and AIS thorax/abdominal <3 and/or AIS lower extremity < 4.
- Subgroup 2: subdivide the population into two groups: with or without anticoagulation treatment before trauma.

- Subgroup 3: subdivide the population into two groups: with or without trauma-induced coagulopathy.
- Subgroup 4: subdivide the dataset in prehospital settings and in-hospital settings.
- Subgroup 5: All analysis and results will be present into two subgroups: missing data imputed and missing data excluded with the complete case analysis.
- Subgroup 6: The investigators will test the heterogenicity of the performance parameters of each centre and the investigators will potentially exclude data from centre with homogeneous case mixes.
- Subgroup 7: subdivide the population into two groups: low-volume prehospital fluid replacement (<1500 ml) and High-volume prehospital fluid replacement (>1500ml).

5.4 Statistical Software

All analyses will be performed using STATA software (version 16.0; Stata Corp, College Station, TX, USA).

6. Discussion

Due to the study population (STR), which is partly integrated into the German DGU-Register, the investigators expect good transportability of the TASH score to the Swiss Trauma Registry in terms of overall performance, discrimination and calibration. The ABC score should show lowers results in terms of discrimination due to its validation on small cohorts exclusively in North America. The new BATT score predicting death due to bleeding has been validated on a large English cohort of more than 100,000 patients. It identifies all patients with haemorrhage and not only patients who have received a massive transfusion subject to survival bias. In this context, the BATT score provides good discrimination with only simple physiological variables available at the trauma scene. In case of its external validation on the STR as part of our study, its feasibility would make its clinical utility superior to other pre-existing scores, while identifying a greater number of patients requiring early management. Its application would activate a massive transfusion plan directly at the trauma scene and save precious time.

7. Conclusion

This SAP presents the principles of analysis of the MTP study and discusses its major methodologic and statistical concerns. The investigators hope that the results of the MTP study will be as transparent and robust as possible, so that the investigators minimised the risk of outcome reporting bias and data-driven results.

8. Tables and Figures

Table 1. Overview of all variables requested from the STR for the MTP study.

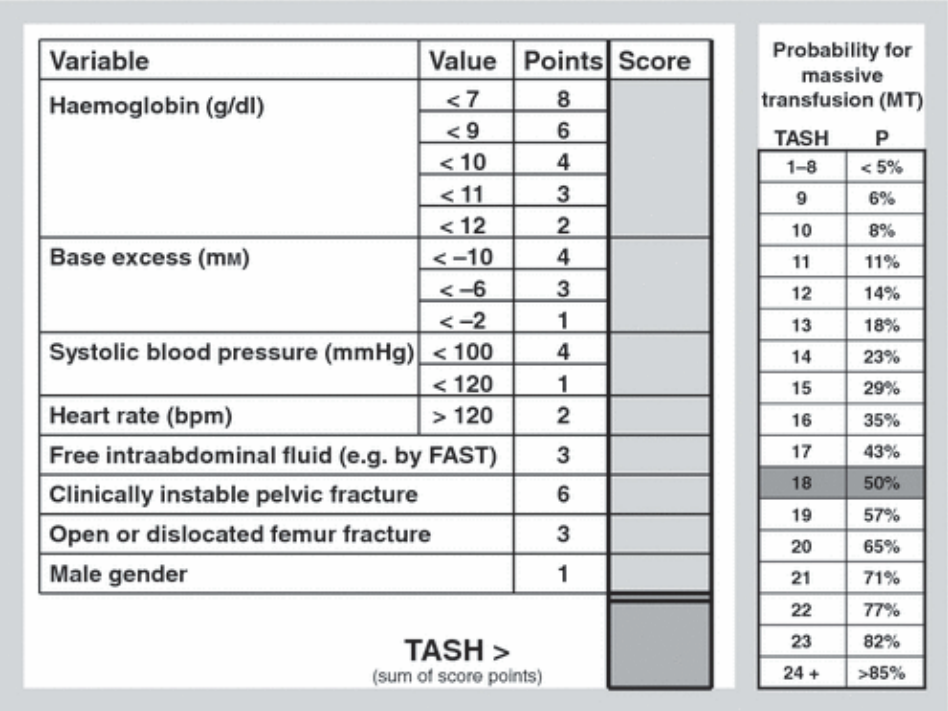
Variable	Prehospital	In-hospital Trauma room	First 24 hours
Demographics			
Age	X		
Gender	X		
Type of accident	X		
Mechanism of Injury	X		
Accident date	X		
Accident time	X		
Medical past	X		
Arrival on scene (paramedics, date/time)	X		
Arrival on scene (medics, date/time)	X		
Physician Staffed Ambulance (yes/no)	X		
Hospital Arrival (date/time)		X	
Clinical examination (first measures recorded)			
Heart Rate	X	X	
Systolic blood pressure	X	X	
Respiratory rate	X	X	
Pulse oximetry	X	X	
Temperature	X	X	
Glasgow Coma Scale	X	X	
Cardiopulmonary Reanimation	X	X	
Biological parameters			
Haemoglobin		X	
Platelets		X	
Lactates		X	
TP		X	

INR		X	
PTT		X	
Fibrinogen		X	
Base excess		X	
Therapy			
Vasoactive drugs (doses, type)		X	
Tranexamic acid (doses, date/time)	X	X	
Vitamin K (doses, date/time)		X	
rFVIIa		X	
Fibrinogen (doses, date/time)		X	
Platelets units (number, date/time)		X	
Red Blood Cell (number, date/time)		X	
prothrombin complex concentrate		X	
Fresh frozen plasma (number, date/time)		X	
Imaging			
Type of Imaging		X	
CT or FAST positive for free fluid		X	
Outcome			
Date and time of death			X
Early death (<12 hours)	X	X	X
Early death (< 24h)			X
Massive Transfusion (defined by 10 RBC/24h)			X
Diagnosis			
Code AIS		X	
Final ISS		X	
Scores			
TASH Score	X	X	
ABC Score	X	X	
BATT Score	X	X	

Table 2. Summarize of potential baseline characteristics.

Age, mean (SD) - ≥ 65 years old, N (%) - < 65 years old, N (%) Sex male, N (%) Mechanism of Injury: N (%) - Penetrating - Blunt Circumstances, N (%) - Road traffic Injury ➢ Car ➢ Motorcycle ➢ Bicycle ➢ Pedestrian ➢ Other (train, boat) - Fall ➢ > 3 meters ➢ < 3 meters ➢ Unclear - Gunshot - Stabbing - Explosion - Avalanche - Other - Unknown Physician staffed ambulance, N (%)	Prehospital SBP, mean (SD) - SBP < 90 mmHg, N (%) - SBP >90 mmHg, N, (%) Prehospital HR, mean (SD) - HR > 120/min, N (%) - HR < 120/min, N (%) Prehospital GCS, N (%) - 3-8 - 9-12 - 13-15 Prehospital CPR, N (%) ISS mean (SD) ISS by categories, N (%) - 9-15 - 16-24 - 25-34 - ≥ 35 Overall AIS score ≥3, N (%) Severe head injury (AIS head ≥3), N (%)	ABC score, mean (SD) 0-1, N (%) 2-4, N (%) TASH score, mean (SD) - 0-17, N (%) - 18-31, N (%) BATT score, mean (SD) - 0-7, N (%) - 8-12, N (%) Death due to bleeding, N (%) Massive transfusion, N (%) Early Death (<24h), N (%) - < 12h, N (%) - 12-24 h, N (%)

Figure 1. TASH score[2]



Variable	Value	Points	Score
Haemoglobin (g/dl)	< 7	8	
	< 9	6	
	< 10	4	
	< 11	3	
	< 12	2	
Base excess (mM)	< –10	4	
	< –6	3	
	< –2	1	
Systolic blood pressure (mmHg)	< 100	4	
	< 120	1	
Heart rate (bpm)	> 120	2	
Free intraabdominal fluid (e.g. by FAST)		3	
Clinically instable pelvic fracture		6	
Open or dislocated femur fracture		3	
Male gender		1	

TASH >
(sum of score points)

Probability for massive transfusion (MT)

TASH	P
1–8	< 5%
9	6%
10	8%
11	11%
12	14%
13	18%
14	23%
15	29%
16	35%
17	43%
18	50%
19	57%
20	65%
21	71%
22	77%
23	82%
24 +	>85%

Figure 2. ABC score[3]

Variable	Value	Points
Penetrating mechanism	Positive	**+ 1**
	Negative	**0**
Systolic Blood Pressure	≤ 90 mmHg	**+ 1**
	< 90 mmHg	**0**
Heart Rate	≥120 bpm	**+ 1**
	<120 bpm	**0**
FAST	Positive	**+1**
	Negative	**0**
ABC score positive for high risk of massive transfusion if ≥ 2 points		

References

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