

Table 1: TETHYS Study Flow Diagram

Time Procedure	Screening: at hospital admission	T0 (Baseline): emergency room until IP treatment start	T1: First 24 hours after IP treatment start #	T2: post-traumatic day 1 [#] -3 (morning)	T3: post-traumatic day 4-7 (morning)	T4 [§] : day 90 after randomization
Inclusion / exclusion criteria	X					
Randomization		X				
Demographic data & medical history	X					
Anamnesis & concomitant diseases (only ongoing and relevant resolved)	X					
Date and time of hospital admission	X					
Blunt / penetrating trauma	X					
Injury characteristics	X					
Fluid input (colloids, crystalloids) after trauma injury and until hospital admission	X					
Surgery due to traumatic injury			X	X	X	
• Type of surgery						

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- Date - Time of skin incision / time of skin suture						
SCr [mg/dl] SCr-based eGFR [ml/min] Cystatin-C [mg/dl] Cystatin-C based eGFR [ml/min] Cystatin-C-based mean eGFR [ml/min] (calculated from the highest cystatin-C level during day 1-3) AKIN score (calculated) Highest AKIN stage reached on each day (during the first week) (calculated) RIFLE score (calculated) Urine output (if available)		X	X*	X	X [¶]	
C-reactive protein [mg/L]		X	X*	X		
Platelet count [μ/L] INR		X	X*	X		

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aPTT [s]						
pCO ₂ [mmHg]						
pO ₂ [mmHg]						
HCO ₃ ⁻ [mmol/l]						
SaO ₂ [%]						
pH		X	X*	X		
Base Excess [mEq/l]						
Hb [g/dl]						
Hct [%]						
Lactate [mmol/l]						
ScvO ₂ [%] (if available)		X	X*	X		
Na ⁺ [mmol/l]						
K ⁺ [mmol/l]						
Ca ²⁺ [mmol/l]		X	X*	X		
Cl ⁻ [mmol/l]						

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Administered IP volume [ml]		X	X			
Fluid input [ml] (incl. every i.v. medication, applied blood products)		X	X	X	X	
Fluid output [ml] (incl. drainage, urine output, estimated blood loss)						
Temperature [°C]		X	X	X	X	
MAP [mmHg] (calculated)						
HR [beats/min]						
SAP [mmHg]		X	X*	X	X	
DAP [mmHg]						
CVP [mmHg] (if available)						

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Haemodynamics as required to determine volume responsiveness (one variable if applicable) MAP [mmHg] SV [ml] SVV [%] PPV [%] SVI [ml/min ²]		During duration of IP administration to assess volume responsiveness				
Mechanical ventilation	X	X	X	X	X	
Use of RRT			X	X	X	X
Antibiotics						
Contrast agents		X	X	X	X	
Diuretics						
Crystalloid (including basal infusion) / albumin		X	X	X	X	
- Administered drug - Volume						
Vasoactive / inotropic drugs		X	X	X	X	
- Administered drug - Dosage/ volume						

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Fibrinogen / PCC / Factor XIII • Administered drug • Dosage/ volume		X	X	X	X	
Applied blood products [ml] • Administered drug • Dosage/ volume		X	X	X	X	
(Serious) adverse events		continuously				
Date and time of hospital discharge					At hospital discharge	
Fulfilment of fit for discharge criteria from hospital					Daily until fulfillment	X
Date of ICU admission		At ICU admission				
Date and time of discharge from ICU				At ICU discharge		
Fulfilment of fit for ICU discharge criteria				Daily until fulfillment		X
Mortality (in-hospital / out of hospital)				X	X	X
Study termination		At termination				

* at least every 6 hours

#: in case assessment of timepoints T1 and T2 (day 1) are within a timespan of max. 2 hours only one assessment per variable has to be done to minimize intervention for the patient, otherwise deemed clinically required.

§: a lag time of ±14 days for the conduct of this follow-up contact is accepted, to account difficulties in obtaining data due to potential causes for delay (e.g., mail delay, or patient's inability to travel) / ¶: except cystatin-C

Table 2: Secondary variables

Safety parameters	Efficacy parameters	Other variables
Renal function • Serum Creatinine and method of determination (colorimetric or enzymatic) • Cystatin-C • Serum Creatinine-based eGFR • Cystatin-C-based eGFR¹ • Cystatin-C-based mean eGFR (calculated from the highest cystatin-C level during day 1-3)¹ • AKIN score² • RIFLE stage² • Urine output (if available) Coagulation • Platelet count • International normalized ratio • Activated partial thromboplastin time Inflammation • C-reactive protein Adverse events • (Serious) adverse events / reactions Outcome • Length of stay (LOS): ▫ LOS in the hospital ▫ LOS in the intensive care unit³ ▫ Fulfillment of Fit for discharge from ICU/ hospital⁴ • Hours on mechanical ventilation • In-hospital / out of hospital mortality (incl. cause) • Days on Renal Replacement Therapy	Fluid administration • Administration of IP volume Fluid balance • Fluid input and output Hemodynamics/vital signs • Heart rate • Mean arterial pressure (MAP) • Systolic arterial blood pressure • Diastolic arterial blood pressure • Central venous pressure³ <i>at least one of the following parameters (volume algorithm):</i> • Stroke volume (SV) • Stroke volume variation (SVV) • Stroke volume index (SVI) • Pulse pressure variation (PPV) • Mean arterial blood pressure (MAP) Laboratory data • Arterial (preferred) blood gas analysis ▫ Partial pressure of carbon dioxide ▫ Partial pressure of oxygen ▫ Bicarbonate ▫ Arterial oxygen saturation ▫ pH ▫ Base Excess ▫ Lactate ▫ Hemoglobin ▫ Hematocrit • Central venous oxygen saturation³ • Serum electrolytes ▫ Sodium ▫ Potassium ▫ Calcium ▫ Chloride	Demographic data and medical history • Age • Gender • Height • Weight • Ethnicity • Anamnesis & concomitant diseases (only ongoing and relevant resolved) • Fluid input from trauma injury until hospital admission Trauma related data • Blunt / penetrating trauma • Injury characteristics ▫ Injury Severity Score ▫ Glasgow Coma Scale • Surgery due to traumatic injury ▫ Type of surgery Concomitant medication • Vasoactive/ inotropic drugs • Amount of transfused blood products [ml] including specification (if available) • Coagulation factors (i.e., fibrinogen/ PCC/ factor XIII) • Antibiotic therapy • Contrast agents • Diuretics • Crystalloid solutions / albumin (incl basal infusion)

¹ calculated from highest cystatin-C level on day 1-3, or hospital discharge (whatever occurs first)

² according to Bagshaw et al.³¹. Missing baseline creatinine levels will be estimated according to the MDRD equation²¹

³ if applicable / if available

⁴ As defined by Marshall et al.³²