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Study Identification No: HC-G-H-1209

NCT02715466

EudraCT No: 2015-000057-20

Prospective, randomized, controlled, double-blind, multi-centric, international study on the efficacy and safety of an early target-controlled plasma volume replacement therapy with a balanced gelatin solution vs. a balanced electrolyte solution in patients with severe sepsis / septic shock

GENIUS (**GE**LATIN I**N** I**C**U AND **S**EPSIS)

Statistical Analysis Plan

Final Analysis

Version: Final 2.0

Date: 05JUL2022

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Table of Contents

1 Introduction

1.1 Preface

The objective of this document is to detail the statistical methodology to be used for the final statistical analysis of the GENIUS study (**Ge**lati**n i**n IC**U** and **S**epsis).

The statistical analysis plan is based on the following information and documents:

Study Protocol	2015-06-26 – Version 1.0
Amendments to Study Protocol	2015-11-30 – Version 2.0 incorporating local Amendment No. 1 - Austria dated 2015-09-30, local Amendment No. 1 - Czech Republic dated 2015-09-22, local Amendment No. 1 - Germany dated 2015-10-09, global Amendment No.1 dated 2015-11-30 2017-05-02 – Version 3.0 incorporating global Amendment No.2 dated 2017-05-02 2018-07-20 – Version 4.0 incorporating global Amendment No.3 dated 2018-07-20 2020-01-10 – Version 5.0 incorporating global Amendment No. 4.0 dated 2020-01-10 2020-07-16 – Version 6.0 incorporating global Amendment No. 5.0 dated 2020-07-16

1.2 Timing of statistical analyses

The following statistical analyses are planned for this study:

- Final analysis: the final unblinded analysis will take place after last patient out, the Blind Data Review Meeting (BDRM) is performed, and the database is locked.

2 Modification History

2.1 Changes to the study protocol

The first version of the statistical analysis plan (SAP) corresponded to protocol version 6.0.

Due to the premature termination of the study recommended by the data safety monitoring board (DSMB) on 8th of December 2021, the interim analysis (IA) for sample size recalculation (SSR) as planned in the study protocol is obsolete and thus only the final analysis of the study will be presented.

The study populations defined on protocol version 6.0 section 14.8 are adapted in this document. The full analysis set was replaced by the safety set and the per protocol set is not taking into account the criteria of stopping of treatment due to adverse reaction.

Moreover, the time unit used for endpoints as the time to HDS will be changed from minutes to hours because it is expected that no patient is stabilized within minutes.

More subgroup analyses were included in section 5.4 of this SAP.

Additional changes to the analyses planned in the study protocol were included in this second version of the SAP, as described in section below. Main updates were related to the discussions during the Blind Data Review Meeting (BDRM).

2.2 Changes to previous SAP versions

This is the second version of the SAP. The following main changes were implemented compared to first version dated 12Jan2022:

- More details were added about the major protocol deviations (PDs) defined during the BDRM and the analyses to be repeated on the Per Protocol (PP) set. Details are specified in section 4 and section 6.2. One subgroup was added as a result of the discussions in the BDRM, please refer to section 5.4. Additionally, categories for SOFA were updated after the BDRM.
- Some treatment comparisons for secondary efficacy analyses were removed due to the high quantity of missing data, please refer to section 10.2. Additionally, MANOVA analyses specified in section 12 were removed due to the same reason.
- The calculation of the total score for the Acute Physiology and Chronic Health Evaluation II (APACHE II), the Sequential Organ Failure Assessment (SOFA), and the Simplified Acute Physiology Score II (SAPS II) was modified including missing values rules. Updates are specified in the respective appendices.
- Summary statistics on overall dosing for concomitant medications was removed, expect for crystalloid solutions, due to a lack of standardization to collect the doses in the electronic case report form (eCRF).
- Kidney Disease Improving Global Outcome (KDIGO) score calculation was adapted considering only serum creatinine values without urine output.
- Additionally minor modifications on outputs layout were included to improve the interpretation of the study results.

3 Study Design

Indication	Hypovolaemia in Severe Sepsis / Septic Shock
Design	Prospective, randomized, controlled, double-blind, multi-centric international study with two parallel groups
Phase	IV
Primary Objective	To investigate the efficacy of early goal directed fluid management of a combination of a gelatin and crystalloid regime in comparison to a pure crystalloid regime in achieving haemodynamic stability (HDS) in patients with severe sepsis / septic shock

Secondary Objective	Investigation of safety and further efficacy parameters of the applied fluid regimes
Treatments	Investigational medicinal test product (gelatin group): Gelaspan (plasma adapted gelatin solution for infusion) To be administered in combination with background medication (non investigational medicinal product: open-label Sterofundin ISO; a plasma adapted electrolyte solution) in a ratio of 1:1 (gelatin:electrolyte) Investigational medicinal reference product (crystalloid group): Sterofundin ISO (plasma adapted electrolyte solution) To be administered in combination with background medication (non investigational medicinal product: open-label Sterofundin ISO; a plasma adapted electrolyte solution) in a ratio of 1:1
Number of patients	N = 608 patients with n=304 patients in the Gelatin and Crystalloid group, respectively.
Planned enrolment	Participating countries: Austria, Czech Republic, France, Germany, Spain, Hungary. Up to 15 sites

3.1 Sample size estimation

The primary variable is the time to first / initial HDS, and it was used to calculate the sample size. The data of a study investigating a hydroxyethyl-starch (HES) solution (Guidet et al., 2012; CRYSTMAS-trial) served as the basis for the sample size calculation. It was however a comparison of a HES-solution with sodium chloride and the results were only an orientation and therefore an interim analysis for sample size recalculation was planned which is obsolete due to the premature termination of the study by the DSMB.

Sample size calculation using the software nQuery and nTerim 2.0 resulted in a sample size of 608 patients in total. It was based on the following assumptions:

- effect size (difference of means / common standard deviation) = 0.25 with difference in means = - 2.5 h and common standard deviation = 10 h
- error of 1st kind α = 5% (two-sided)
- power = 80%

Applying a t- test for group comparison yielded a sample size of 253 patients per group for HDS in minutes. Taking a drop out rate of 20% into account, a sample size of 304 patients per group (i.e. 608

patients in total) is needed. Drop-out patients are defined as those patients who do not receive any investigational product.

Withdrawn patients who did not receive any Investigational product (IP) will not be replaced because they are considered in the dropout rate.

3.2 Randomisation, blinding and unblinding procedures

Patients were randomized to either treatment in a 1:1 ratio.

The list of treatment assignments considering the stratification for site and red blood cell (RBC)s pre-treatment were generated by a statistician (not involved in the study data analyses) comprised of consecutive blocks with the order of assignments chosen at random (e.g. random permuted block of size 4, 6 or 8). The randomization lists (initial and new sites) were prepared prior to the initiation of the study site and remained with the statistician. A signed copy of the randomization lists was given to the qualified person for IPs (sponsor), who was responsible for the blinding of the samples. Based on the randomization lists the statistician also issued sets of emergency envelopes for each participating site for emergency unblinding. The sponsor, i.e. qualified person study supply and drug safety officer received a complete set of emergency envelopes for emergency situations. In addition, the biometrician of the Data Safety Monitoring Board (DSMB) received the de-blinding envelopes for each patient, in case un-blinding upon request of the DSMB was necessary. The same procedure would be performed in case of new study sites and recruitment of more patients per sites as initially expected.

After closure of the database and determination of the analysis populations (in a blinded data review meeting if appropriate) the study will be unblinded.

The population was stratified with regard to site and RBC pre-treatment 24 h prior to randomization. These stratification variables will be included as covariate in the primary analysis (according to CPMP/EWP/2863/99).

4 Analysis Sets

The statistical analyses and presentation of data will be based on the following analysis sets:

- **Enrolled Analysis Set**

  It includes all patients with an informed consent signed by patient, legal representative or authorized person or deferred consent according to local legislation / requirements approved by the ethic committee / competent authority.

- **Intent-To-Treat Set (ITT)**

  The ITT set includes all patients randomized. Following the intent-to-treat (ITT) principle all patients will be analyzed according to the treatment group to which they were randomized. This population will be used for the description of demographics and other baseline characteristics, and for the assessment of efficacy endpoints.

- **Safety Analysis Set (SAF)**

The SAF includes all ITT patients treated at least once with the study medication. All patients will be analyzed according to the treatment they received. This population will be used mainly for the safety endpoints and exposure analyses.

- **Per Protocol Set (PP)**

  The PP set includes all patients from the SAF set, excluding patients with major protocol deviations (please refer to section 6.2). All patients will be analyzed according to the treatment they received. The assessment of protocol deviations and the categorization into major and minor deviations was performed before unblinding during the BDRM. As the difference between the PP set and the SAF set is higher than 10% of the patients included in SAF, main analyses based on SAF will be repeated in the PP set. As the ITT and the SAF set contain the same number of patients for this study (all patients randomized were treated), the difference between the PP set and the ITT set is the same, also greater than 10% of the patients included in ITT. Therefore, main analyses based on ITT will be repeated in PP set. Minor protocol deviations do not lead to the exclusion of patients from any analysis set.

If not otherwise stated in the respective section, the statistical analyses will be performed on the following analysis sets:

Analyses	Enrolled	ITT	SAF	PP
Disposition	✓			
Demographics and background characteristics		✓		(✓)
Exposure and compliance			✓	
Concomitant therapies			✓	(✓)
Primary Efficacy analysis		✓		(✓)
Secondary Efficacy analyses		✓		(✓)
Other/Exploratory Efficacy analyses		✓		(✓)
Safety analyses			✓	(✓)

The symbol (✓) means that the related analyses were optional at the planning of the analyses.

The following analyses will be repeated for the PP set as decided during BDRM discussion:

- Demographics and background characteristics
- Concomitant therapies
  - Antibiotics
  - Colloid therapy (not allowed medication)
- Primary efficacy analyses
- Other / exploratory efficacy analyses
- Safety analyses

Specific TLGs to be repeated on the PP set are included in Table Shells.

5 General Statistical Methods and Definitions

5.1 General statistical methods

The statistical analyses will be presented by treatment group for the different analysis sets as defined in section 4.

In general, continuous variables will be summarised using descriptive statistics, i.e. generally displaying number of patients in the respective analysis population, number of patients with data, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum.

Categorical variables will be summarised by using frequency counts and percentages.

In case at least one parameter in a table has missing values, a row/column with the number of missing values will be added. In case no missing values are documented at all for a table, no missing rows/columns will be presented, even if missing rows/columns are foreseen in the respective table shell.

Individual patient data listings will be provided for all data collected. Listings will be sorted by patient ID, and when appropriate by visit or other identifiers for sequence or type of observation. All listings will present the patient ID, site, treatment group, strata, age, and gender.

Means and medians will be presented with one additional decimal place and standard deviation will be presented with two additional decimal places compared to the original source data. Minimum and maximum values will be presented using the same number of decimal places as the patient data. Percentages will be presented with one decimal place if not otherwise stated.

If the number of patients in a category is 0, then percentage will not be displayed, and only a count of 0 will be shown.

P-values will be reported to 4 decimal places at least. Values less than 0.0001 will be displayed as <0.0001. Values above 0.9995 will be displayed as 1.0000.

If not otherwise specified, all statistical tests will be two-sided with a significance level of 5%. The confidence level for the calculation of confidence intervals will be 95%, respectively.

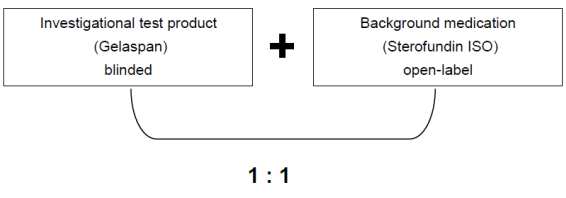
5.2 Assignment to analysis/treatment groups

Treatments will be labelled as follows:

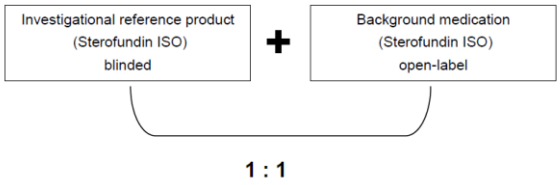
- Gelatin group
- Crystalloid group
- Total (when applicable)

They are defined as:

- Gelatin group:



- Crystalloid group:



5.3 Covariates and strata

The population will be stratified with regards to site and RBC pre-treatment 24 h prior to randomization (yes/no). These stratification variables will be included as covariate in the primary analysis, as will be specified in section 10.1. Frequencies of randomized patients within each stratum will be presented as part of the analysis.

5.4 Subgroups

The following subgroup analyses are planned to be conducted for the primary endpoint:

- Strata (prior RBC treatment, sites)
- Prior RBC treatment as confirmed in the eCRF and not according to assigned stratum
- Administration of fluids 24 h prior randomisation (yes/no)
- Acute Physiology And Chronic Health Evaluation II (APACHE II) total score (algorithm specified in appendix 18.1): < 20 score points, 21-30 score points, > 30 score points. Final categories were confirmed at the BDRM.
- Sepsis-related Organ Failure Assessment (SOFA) total score at baseline (algorithm specified in appendix 18.2): < 10 score points, ≥ 10 score points. Final categories were re-defined at the BDRM.
- Renal assessment from SOFA at baseline: 1-2 vs 3-5. Score 1 is defined as the recorded score 0 in the eCRF that corresponds to the category “Creatinine < 110 umol/L (1.2mg/dL) or urine output >=500 mL/d”. Score 2 corresponds to the recorded score 1 in the eCRF, and so forth.
- Administration of blood products during the study (yes/no)
- Septic shock / severe sepsis at diagnosis
- One occurrence of septic shock or severe sepsis / at least two occurrences of septic shock or severe sepsis (episodes of severe sepsis / septic shock)
- Diagnosis of severe sepsis or septic shock at intensive care unit (ICU) admission / diagnosis of severe sepsis or septic shock during ICU stay
- Country
- Concomitant medication (allowed / not allowed). Please refer to section 9 for further details on the definition of allowed and not allowed concomitant medication. Under allowed medication, only patients that didn’t receive any not allowed medications (i.e. that received only allowed medications) will be included. Not allowed medication subgroup will include patients that received at least one dose of not allowed medication as described in section 9.
- Use of renal replacement therapy (RRT) during the study (yes, no)

- Type of patient (trauma, surgical, medical)

In case a subgroup category has less than 10 patients, descriptive data will be presented but treatment comparisons will not be made for that category.

5.5 Missing data

Every effort will be made to collect all data points in the study. Missing data will not be imputed. Partial and missing dates will be imputed as specified below only to determine if an event is concomitant to the study drug administration or not, assuming the most conservative approach. Missing data are only those which are required as defined in the protocol and had not been recorded in the eCRF during study participation of a patient. For example, in case a patient terminated the study on day 7, all data thereafter are not counted as missing.

Partial or missing dates and times

Where the start date of an adverse event or medical condition (administration of a concomitant medication needed) is missing or partially missing, the event will be assumed to be started after the start of study medication, unless there is clear evidence (through comparison of partial dates/times) to suggest otherwise. Duration of an event with missing start or end date will remain as missing.

In case of a partial or missing end date the medical condition will be assumed to be ongoing after start of study medication except if the partial date indicates that the condition stopped prior to start of study medication.

Remaining missing dates will be imputed as follows:

For event start date, imputation rule is to conservatively capture events with missing start dates as occurred during treatment:

- If “day” is the only missing field, impute the “day” as the first dose date if their “month” are the same. Otherwise impute the “day” as the first day of the month documented.
- If “day” and “month” are the only missing fields, impute the “day” and “month” as the first dose date if their “year” is the same. Otherwise impute the “day” and “month” as the first of January of the year documented.
- If “day”, “month”, and “year” are all missing, to be conservative, the event will be assumed to occur on the same day as the first dose was administered.

For event end date, imputation rule is to conservatively capture events with missing end dates as occurred during treatment:

- If “day” is the only missing field, impute the “day” as the last day of the month documented if their “month” are the same.
- If “day” and “month” are the only missing fields, impute the “day” and “month” as December 31 of the year, if the patient is alive at that date. Otherwise impute the date of death.
- If “day”, “month”, and “year” are all missing, to be conservative, the event will be assumed to be ongoing at the end of the study for the respective patient.

Dates as collected will be presented in data listings.

Outliers

No outliers were identified for the primary endpoint variable ‘time to HDS’.

For laboratory parameters, as specified in section 11.3, box plots by visit will be performed for the change from baseline in order to detect the outliers. Outliers were detected and checked by data management, and specific box plots for serum creatinine will be repeated excluding change from baseline values greater or lower than 200 umol/L (as agreed during the BDRM).

5.6 Observation and analysis times

Study days

Study day is defined as the number of days since first randomized treatment administration, and is calculated as:

Study day = assessment date – date of first randomized treatment administration + 1.

Therefore, the date of the first administration of randomized treatment will be Day 1.

Study time

Study time is defined as the number of minutes since the time of the first randomized treatment to the assessment time. The study time in hours will also be derived.

Definition of baseline values or first assessment

The baseline value is defined to be the last value which was assessed before first study drug administration. For the parameters where values were not measured / available at baseline, the value of the first assessment measured/available shortly after treatment start will be used.

5.7 Multiple Comparison/Multiplicity

All tests will be conducted with an error $\alpha = 0.05$ two-sided, unless otherwise specified.

Tests of all secondary variables will be carried out in the area of exploratory data analysis if applicable. Therefore, corresponding p-values are to be regarded as exploratory ones and no adjustments for multiple testing will be made.

6 Patient Accounting and Disposition

6.1 Patient accounting

The number and relative frequencies of patient in each analysis set as defined in section 4 will be presented overall and by randomized treatment (if applicable), and will be listed. Additionally, the number of patients randomized per country and site will be presented by treatment group.

Eligibility criteria will be presented in a data listing, containing the information of the informed consent(s).

6.1 Disposition and withdrawals

The number and relative frequency will be presented by treatment group based on all enrolled patients for

- screening phase patients, eligible patients, and failures
- patients randomized

- first treatment phase and second treatment phase patients, each separately, and both phases
- patients who discontinued the treatment due to AE
- patients who prematurely discontinued the study, related reasons, and person who took the decision
- patients who achieved HDS and not, and patients with missing HDS status
- patients who entered and completed follow-up 1, follow-up 2, and follow-up 1 and 2
- patients that completed the study
- patients with treatment code broken

A listing with disposition information will be presented for all enrolled patients. Additionally, a disposition table by country will be presented.

6.2 Major protocol deviations

A protocol deviation (PD) is any noncompliance with the study protocol, Good Clinical Practice (GCP), or Manual of Procedures (MOP) requirements. The PD which impacts the interpretability of the main study results and assessment of the treatment effect will be marked as major protocol deviation. A pre-selection of all protocol deviations was reviewed and finally classified as either major or minor during the BDRM. Please refer to BDRM minutes for a final assessment on those.

Major PDs were identified for the following categories:

- Concomitant medication
- In/Exclusion criteria
- IP storage
- IP treatment/Volume algorithm
- Primary endpoint
- Randomization

The number and relative frequency of patients with major protocol deviations leading to exclusion from the Per Protocol set will be presented by treatment group for all patients of the ITT. Additionally, patients with major protocol deviations related to Covid-19 pandemic situation will be also presented.

A listing with all protocol deviations will be presented based on ITT set.

7 Demographics and Background Characteristics

Demographic and baseline characteristics as specified in detail below will be presented descriptively by treatment group based on ITT set.

7.1 Demographics

The following demographic characteristics will be presented by frequencies or summary statistics, as applicable:

- Gender (male/female)
- Age (years) as entered in the electronic case report form (eCRF)
- Age ranges (18-64, 65-84, ≥85 years)

- Race (Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, White)
- Weight (kg) at baseline
- Height (cm) at baseline
- Body mass index (BMI) (kg/m^2) at baseline as automatically calculated within the eCRF
- Body surface area (BSA) at baseline [m^2]: $0.007184\ x\ Weight^{0.425}\ [kg]\ x\ Height^{0.725}[cm]$
- Temperature (C) overall, minimum and maximum at baseline
- Childbearing potential data

A data listing containing the mentioned demographic variables will be presented based on ITT set.

7.2 Disease characteristics

A frequency table displaying the type of patient (trauma, medical or surgical patient) will be provided together with information on the type of sepsis diagnosed. The time (min) from the time of admission to ICU to randomization and the time (min) from diagnosis to ICU admission will be also derived and presented descriptively for those patients where applicable. The time from diagnosis to randomization will also be summarized for patients that are on the ICU at the time of trial participation, i.e. diagnosis of severe sepsis/septic shock on ICU and following randomization.

Additionally, summary statistics and frequencies will be provided for the following parameters of anamnesis:

- Simplified Acute Physiology Score II (SAPS II) score, APACHE II, and SOFA total score at baseline. Please refer to appendices 18.1, 18.2, and 18.3 for the specification of the APACHE II, SOFA, and SAPS II score calculation respectively.
- Fluid input in the 24 h prior to randomization: yes/no and amount (ml)
- Antibiotic therapy prior to randomization: yes/no
- RBC therapy 24 hours prior randomization: yes/no
- Lactate prior treatment (mmol/L)
- Fluid responsiveness for inclusion: type of test (Fluid challenge (FC) or Passive leg raising (PLR)), volume (ml) by type of test, Mean arterial pressure (MAP) change (%), MAP before PLR/FC (mmHg), MAP after PLR/FC (mmHg)

A correlation analyses among SAPS II, APACHE II and SOFA total scores at baseline will be done thought a correlation test. Pearson correlation coefficients and related p-values will be tabulated.

Additional details on disease characteristics parameters, as origin of sepsis or causative organism of infection, will be provided in a data listing. Details of fluid input in the 24h prior to randomization and antibiotic therapy prior to randomization will also be presented in data listings.

7.3 Medical history

Past and ongoing medical history is be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 24.1, and will be summarized presenting numbers and frequencies by primary

System Organ Class (SOC) and Preferred Term (PT) by treatment group. Past medical history are the disorders not ongoing during the study conduct.

If patients have more than one disease within a SOC or PT they will be counted only once for the respective SOC or PT.

8 Exposure

The SAF set will be used to present exposure analyses.

8.1 Treatment groups

Treatments will be labelled as follows:

- Gelatin group
- Crystalloid group
- Total

The number and percentage of patients will be presented by treatment group based on SAF set. Treatment-related summaries will be presented separately for the IP (first and second treatment phase together) and the background medication (BG).

8.2 Dosage and Treatment duration

The IP treatment is defined for two treatment phases:

The **first treatment phase** starts with randomization and ends in general at the time a haemodynamic monitoring system is in place or HDS has already been achieved and confirmed.

If the HDS criteria are not fulfilled during this treatment phase until having a haemodynamic monitoring system in place the patient enters the second treatment phase. For this a haemodynamic monitoring system able to directly measure cardiac output (i.e. Stroke volume index (SVI)) has to be in place. First treatment phase is not needed when a hemodynamic system is already in place at IP treatment start.

The **second treatment phase** starts with the time a haemodynamic monitoring system is in place and ends when HDS occurs for the first time or 48 hours after randomization, whatever occurs first.

Treatment with blinded IPs in combination with unblinded background medication ends with the achievement of first / initial HDS, achievement of maximum daily dose of 30 ml/kg for the IPs or after 48 h after randomization, whatever occurs first.

The total IP/BG treatment duration will be calculated in hours as the complete time of the two treatment phases:

> Total Treatment duration (hours) = min(time(confirmed* HDS, maximum daily dose, 48 h after randomization))-time(treatment start)

**confirmed covers the time from initial HDS until end of the 4 hours confirmation period.*

Summary tables by treatment group will be provided as applicable for the following variables:

- Total treatment duration (hours) by IP and BG and total

- Total volume of study fluids administered according to the volume algorithm needed to achieve first HDS [ml] by IP and BG and total
- Total volume of fluids over study time [ml] (max. until 48 h after randomization) by IP and BG and total
- Mean volume of fluid bottles per fluid administration [ml] (IP, BG, total)
- Total of administered bottles by IP and BG and total
- Total volume of additional administered crystalloid solutions [ml]
- Fluid intake [ml] 0-24h and 24-48h
- Fluid output [ml] 0-24h and 24-48h
- Fluid balance = Fluid input [ml] – fluid output [ml] 0-24h and 24-48h
- Fluid overload [%] = [(fluid intake – fluid output)/weight] x 100 0-24h and 24-48h
- Total number of drug interruptions/stops/changes due to AE

A data listing including the fluid administrations according to volume algorithm will be presented for the first and second treatment phase. Similarly, a data listing including information about the assessment of fluid responsiveness upon PLR/MAP and haemodynamic monitoring/SVI will be presented.

9 Concomitant Therapies

Concomitant medications are coded according to the World Health Organization drug dictionary (WHO-Drug version 2021Q2_B3_Global) and stored with generic (preferred) names.

Medications that were taken after the first dose of randomized treatment will be considered concomitant medications. Missing or partly missing stop dates will be imputed using the rules defined in section 5.5. The number and frequency concomitant medications will be given per medication preferred name based on SAF set. If a patient has received more than 1 drug within a preferred name, he/she will be counted only once for this preferred name.

Additionally, overall duration for each concomitant therapy will be summarized, and total volume for crystalloid solutions therapy will be also summarized.

One concomitant medication table per type of therapy will be presented: antibiotic agents, anticoagulation agents, blood products, contrast agents, crystalloid solutions, inotropic agents, nephrotoxic agents, vasopressors, other concomitant medication.

Data listings for concomitant medications will be also presented indicating administration and dosing details.

9.1 Not allowed concomitant therapies

The following concomitant medications are not allowed for this study (please refer to section 9.2 of the study protocol):

- During the treatment period, that is between randomization and until the achievement of HDS or 48 h after randomization, whatever occurs first, administration of other colloid volume replacement agents (e.g. other gelatin solutions, albumin, dextran, HES solutions) aside from colloids to be administered according to the volume algorithm is NOT allowed.

- Beyond the treatment period, that is between HDS or 48 h after randomization and ICU discharge or day 28, whatever occurs first administration of colloid volume replacements (i.e. gelatin solutions, albumin, dextran, HES solutions or other colloid solutions) is NOT allowed; i.e. only crystalloid solutions are allowed in this study period.

Final classification of allowed and not allowed medications was defined during the BDRM. Not allowed medications leading to the corresponding exclusion from the PP set are:

- Colloid solutions (including Gelatin solutions) that are applied after randomization until ICU discharge / day 28 whatever occurs first will lead to major PD (no exceptions)
- Albumin that was applied between randomization and 48h after randomization will lead to major PD
- Albumin with different indication than solely albumin substitution, albumin supplementation, liver failure or hypoalbuminemia from timepoint 48h after randomization until ICU discharge/day 28 whatever occurs first will lead to major PD.

10 Efficacy

Efficacy analyses will be presented based on ITT set, unless otherwise specified.

10.1 Primary efficacy analysis

The primary objective is the verification of the difference in the time to achieve first / initial HDS using a gelatin solution combined with a balanced electrolyte solution (gelatin group) versus a balanced electrolyte solution (crystalloid group), so that the following hypothesis needs to be tested:

$$H_0: HDS_{gelatin} = HDS_{crystalloid}$$
$$H_1: HDS_{gelatin} \neq HDS_{crystalloid}$$

The primary efficacy endpoint is then defined as the time from first administration of IPs to first achievement of confirmed HDS (time to HDS at timepoint 0h after confirmation at 4h) in hours. A patient is thereby considered as haemodynamically stable, if MAP > 65 mmHg and at least two of the following three criteria are fulfilled:

1. Arterial lactate decrease within the last 6 h > 10% or lactate < 2.4 mmol/l
2. Urine production > 0.5 ml/kg/h
3. $ScvO_2$ > 70%

Once these criteria are fulfilled for the first time, treatment with study fluids temporarily stops and the patient is monitored at 2 and 4 h after the first fulfilment of the haemodynamic stability criteria. If during these 4 hours the patient remains stable (criteria fulfilment) and there is no need to increase inotrope and / or vasopressor therapy and a maximum of 1 l additional study fluids is administered for more than 30 min due to sedation, the patient is considered stable and treatment with fluids definitively stops. The confirmation of the HDS at the 2h and 4h will be selected using the respective timepoints collected in the database. The first 0h time where the criteria for HDS are fulfilled and where HDS was confirmed 2 and 4 hours thereafter will be used for the calculation of the primary parameter, i.e. time to HDS.

Patients that do not achieve HDS will be excluded from the primary endpoint analysis. A second analysis will be done imputing the missing time to HDS values to the worst-case scenario using the worst time to HDS value for the Gelatin group and the best time to HDS value for the Crystalloid group.

Data related to the HDS will be taken from the eCRF page "Haemodynamic parameters (HDS)".

The time to HDS (hours) will be summarized descriptively per treatment group based on the ITT set, and the treatment difference will be analyzed by use of a non-parametric test called Mann-Whitney U-test. The stratification variables will be considered covariates in a second non-parametric analysis of covariance (Van Elteren test). A box plot will also be presented for time to HDS by treatment group, in order to observe groups distributions and detect potential outliers. Moreover, first achieved HDS parameters will be summarized by treatment group at timepoint 0h, 2h and 4h.

A data listing presenting the information collected under the eCRF page "Haemodynamic parameters (HDS)" will be created.

10.2 Secondary efficacy analyses

The development of different parameters is assessed to closely monitor the patient during the acute phase in ICU. These parameters are used to investigate efficacy of the IPs by analysing the development over time.

Initial planned treatment comparisons were going to be made at the last recorded value per patient. However, during the preparation of the BDRM it revealed that patients discontinued at different timepoints. Thus, this analysis is not meaningful from a clinical/statistical perspective. Moreover, the team observed a general high quantity of missing data for timepoints after day 6, where less than 50% of the patients recorded data for the planned parameters in most of the cases. For example, only around 20% of patients in ITT set recorded values of cardiac index during treatment period, and the percentage decreases for cardiac index minimum and maximum after day 3. Therefore, it was agreed to remove the treatment comparisons for these secondary endpoints and simply present the descriptive summaries by visit in an exploratory manner.

In case more than one value per patient, parameter, and timepoint is recorded, only the first non-missing value will be presented in summary tables. All recorded values will be presented in data listings.

Fluid responsiveness

The following parameters will be summarized by treatment group based on ITT set over the different collection timepoints:

- Volume responsiveness upon passive leg raising (PLR) with MAP values and change (%). The first non-missing value recorded per patient and timepoint will be used for the summary.
- Volume responsiveness by SVI with SVI values, SVI change (%) and MAP (mmHg). The first value non-missing recorded per patient and timepoint will be used for the summary.

Haemodynamic parameters

- Mean arterial pressure (MAP) [mmHg]
- Stroke volume index (SVI) [ml/m^2]
- Cardiac index (CI) [l/min/m^2] during treatment period, CI min and CI max for the rest of timepoints

- Central venous pressure (CVP) [mmHg] during treatment period, CVP min and CVP max for the rest of timepoints
- Systolic arterial pressure (SAP) [mmHg] during treatment period, SAP min and SAP max for the rest of timepoints
- Diastolic arterial pressure (DAP) [mmHg] during treatment period, DAP min and DAP max for the rest of timepoints

Parameters assessing tissue oxygenation and acid base balance / blood gas analysis (BGA)

The following parameters will be summarized by treatment group and specimen type (separately and all together) including the change from first assessment based on ITT set:

- Partial pressure of carbon dioxide (pCO_2) [mmHg]
- Partial pressure of oxygen (pO_2) [mmHg]
- Hydrogen carbonate (HCO_3) [mmol/l]
- Arterial oxygen saturation (SaO_2) [%]
- Haemoglobin (Hb) [g/dl]
- Haematocrit (Hct) [%]
- Pondus hydrogenii (pH)
- Base excess (BE) [mEq/l]
- Sodium (Na^+) [mmol/l]
- Potassium (K^+) [mmol/l]
- Calcium (Ca^{2+}) [mmol/l]
- Chloride (Cl^-) [mmol/l]
- Central venous oxygen saturation (ScvO2) [%]
- Lactate [mmol/l]
- Lactate decrease [%]
- Arterial oxygen content (CaO2) [mL/dL] = (1.34×SaO2×Hb) + (0.003×paO2)
- Oxygen delivery (DO2) [ml/min] = 10 × CI × CaO2
- Urine output [mL]

10.3 Other secondary analyses

Other secondary variables will be assessed to compare the patient's status during the treatment period. Secondary target variables will also be evaluated with nonparametric tests according to their scaling, using a Mann-Whitney U-test or Chi-square test. Whereby, in case of a small random sample size or an unbalanced condition, Fisher exact test will be used for the categorical comparisons. The assessment of a statistical test will be finally confirmed following the data available at DBL.

If obtained p-values are lower than α=0.05, then the null hypothesis of an equal treatment effect will be rejected.

Parameters assessing clinical outcome

- Length of stay in ICU (days): date of ICU discharge-date of ICU admission+1
- Length of stay in hospital (days): date of hospital discharge-date of hospital admission+1
- Cumulative days on renal replacement therapy (RRT) during study and follow-up, separately: Trigger for starting RRT will be also summarized over time during the study presenting frequencies for the trigger options and summarizing descriptively the duration of the RRT.
- Number of infection free days
- Number of antibiotic free days
- Number of ventilator free days
- Number of vasopressor free days
- Number of patients that needed mechanical ventilation, and patients with ongoing mechanical ventilation
- Cumulative days on invasive mechanical ventilation
- Total number of new severe sepsis/septic shock per patient, type of sepsis and presence of infection

Time from first IP administration to ICU discharge and to ICU discharge during study will be also analyzed with a Kaplan-Meier plot and treatment comparison will be done with a log-rank test. Patients without ICU discharge fulfilled will be censor to the last time they are known to be in ICU or to their planned end of the study date (i.e. up to day 90 plus 14 days), respectively.

Data listings containing more information about each one of the parameters will be presented.

Additionally, a summary table for the SOFA score measurements and their change from baseline will be presented by treatment group, as well as the corresponding data listing. Similar analyses will be presented for SAPS II and APACHE II data that was collected with prior protocol versions.

Analyses related to the need of RRT therapy will be repeated by the subgroup of SOFA renal score at baseline.

10.4 Exploratory analyses

Exploratory analyses will be presented to compare the current trial definition of severe sepsis and septic shock with the new definitions specified in the article from Mervyn Singer et al, 2016.

Sepsis is newly defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA score ≥ 2 points consequent to the infection. The baseline SOFA score can be assumed to be zero in patients not known to have pre-existing organ dysfunction.

Patients with septic shock can be identified now with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65mmHg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation.

A summary table will present the frequencies of patients with new sepsis/septic shock as recorded in the database and as per new definitions above.

11 Safety

Safety analyses will be presented based on SAF set.

11.1 Adverse events

Adverse events (AE) are coded using MedDRA version 24.1 and presented by primary System Organ Class (SOC) and Preferred Term (PT).

The analysis will focus on the treatment-emergent AEs (TEAE), i.e., AEs which started or worsened on or after the first study medication intake. Additionally, Adverse Reactions (AR) will be analysed, defined as all TEAEs judged by the reporting investigator as having a reasonable causal relationship to the IP. If relationship to study drug is missing, the event will be assessed as unrelated if it started before start of study medication; in all other cases it will be assumed to be related. If seriousness criteria is missing, the event will be considered serious.

Adverse events of special interest (AESIs) are defined as those whose SOC/PT is one of the following list:

- Renal and urinary disorders/Acute kidney injury
- Renal and urinary disorders/Renal failure
- Investigations/Blood creatinine decreased
- Surgical and medical procedures/Renal replacement therapy

Number and frequencies of patients with TEAEs and number of TEAEs will be presented based on SAF set in an overall table and given by SOC and by PT within each SOC for the following:

- All TEAEs by treatment group
- Serious TEAEs by treatment group
- Non-serious TEAEs by treatment group
- All ARs by treatment group
- Non-treatment related TEAEs by treatment group
- Serious ARs by treatment group
- Non-serious ARs by treatment group
- Severe TEAEs by treatment group
- Severe ARs by treatment group
- TEAEs of special interest by treatment group
- ARs of special interest by treatment group
- TEAEs leading to death by treatment group (if occurring in more than 5 patients, otherwise a listing will be sufficient)

- TEAEs leading to study discontinuation by treatment group (if occurring in more than 5 patients, otherwise a listing will be sufficient)
- ARs leading to death by treatment group (if occurring in more than 5 patients, otherwise a listing will be sufficient)
- ARs leading to study discontinuation by treatment group (if occurring in more than 5 patients, otherwise a listing will be sufficient)

Number and frequencies of patients with TEAEs and ARs will be presented by decreasing frequency of the overall group. A patient with more than one event in the same SOC or PT will be counted only once within the respective SOC and PT, respectively.

All TEAEs and ARs will be also presented by maximum severity, PT and SOC and by treatment group. If severity is missing, the event will not be included in the frequency tables presenting events by intensity.

A frequency table by treatment group of the number of patients that died during study (i.e. before ICU discharge or day 28), during follow-up, until follow-up 1, and after follow-up 1 will be presented, and the death cause will be also presented. Additionally, a Kaplan-Meier analysis of time to death within the planned study period (i.e. up to day 90 plus 14 days) and up to the last date patients are known to be alive will be presented separately. Patients that didn't die during the study will be censored to the planned end of study as per study protocol or to the last time they are known to be alive, respectively. Additionally, a Cox regression model over time to death will be analyzed using the time to HDS, the treatment, the prior RBC therapy as confirmed in the eCRF, and the SOFA renal score at baseline as independent variables.

Moreover, a box plot of APACHE II score at baseline by mortality status will be created.

In order to assess a potential relationship between HDS and mortality, a logistic regression over the mortality status (yes/no) will be presented, using the HDS (yes/no), the treatment, the prior RBC therapy as confirmed in the eCRF, and the baseline SOFA renal score as independent variables

Separated data listings for all AEs and all serious AEs will be presented, indicating if the event is an AR.

11.2 Vital signs

Vital signs parameters are assessed within APACHE II parameters (section 7.2) and as part of secondary endpoints (haemodynamic parameters) in section 7.2 and will therefore not be analyzed separately. Only temperature measurements (overall, minimum, and maximum) taken during the treatment course will be summarized additionally.

11.3 Clinical safety laboratory

Summary tables over time by treatment group and box plots will be provided for all haematology and clinical chemistry parameters that were not analyzed as secondary variables (see section 10.2), including the change from the baseline or first assessment value. They are:

- Coagulation parameters: prothrombin time (PT), activated partial thromboplastin time (aPTT), international norm ratio (INR), and site-specific parameters (Innsbruck): fibrinogen, antithrombin (AT), and platelets absolute.
- Hepatic function parameters: total bilirubin

- Renal function parameters: serum creatinine (SCr), serum blood urea nitrogen (BUN), Procalcitonin, and:
    - Creatinine clearance (Ccr) using Cockcroft-Gault-Formula

$$Ccr = \frac{(140 - age)x\ weight\ [kg]}{72\ x\ SCr[mg/dl]}\ x\ (0.85, if\ female)$$

    - SCr-based eGFR using CKD-EPI (SCr)-equation (Inker et al., 2012) until day 7

Sex	SCr	Formula
Female	≤ 0.7mg/dl	144 x (SCr/0.7)$^{-0.329}$ x 0.993^{Age} [x 1.159 if black]
Female	> 0.7mg/dl	144 x (SCr/0.7)$^{-1.209}$ x 0.993^{Age} [x 1.159 if black]
Male	≤ 0.9mg/dl	141 x (SCr/0.9)$^{-0.411}$ x 0.993^{Age} [x 1.159 if black]
Male	> 0.9mg/dl	141 x (SCr/0.9)$^{-1.209}$ x 0.993^{Age} [x 1.159 if black]

Serum creatinine summary and box plot will be repeated for the renal SOFA subgroup defined in section 5.4.

Additionally, serum creatinine and urine output (randomization until 48h) measured during the treatment period will be summarized by timepoint and repeated for the subgroups defined in section 5.4.

11.4 Kidney Disease Improving Global Outcome (KDIGO) score

The KDIGO score calculated as specified in appendix 18.4 will be used as basis for the summary analyses. A shift table with the KDIGO stages during the study period (until day 7) will be presented based on the table specified in appendix 18.4.

KDIGO score values calculated and also the ones collected in the eCRF will be listed.

12 Sensitivity Analyses

Primary endpoint will be also analyzed throughout a survival analysis with Kaplan-Meier estimates and a stratified log-rank test. Patients that do not achieve HDS will be censored to the last HDS assessment date where they were free of the event of interest.

Primary and secondary endpoints will be repeated on the PP set as specified in section 4, as well as demographics and main baseline characteristics outputs and safety analyses.

Additionally, as protocol version 6.0 changed some inclusion/exclusion criteria, primary endpoint analysis for patients that were enrolled with prior protocol versions vs. patients that were enrolled after protocol version 6.0 will be presented.

No outliers are identified in the primary endpoint analysis during the preparation of the BDRM, therefore no further sensitivity analyses without the detected outliers will be presented as needed.

Subgroups analyses on primary endpoint as specified in section 5.4 will be also presented reproducing the analyses planned for this endpoint based on the different subgroup categories. Similar analyses by subgroups will be done for TEAEs, serious TEAEs, mortality and serum creatinine values during treatment period (from randomization until 48h).

Further sensitivity analyses may be defined during the course of the study as applicable.

13 Follow-up analyses

The following variables will be analyzed as part of the follow-up period based on ITT set.

13.1 Follow-up therapies

Data listings and summary statistics will be presented containing information about the follow-up data collected at day 28 and day 90 for:

- Mortality including cause of death, if applicable
- Colloid therapy administered (only day 28)
- Last available serum creatinine data (only day 28)
- Renal replacement therapy (RRT) or new kidney disease including cause, if applicable (only day 90)

13.2 Health Related Quality of Life (HRQoL) 90 days after randomization

Patients' quality of life will be measured by using the HRQoL questionnaire (EQ-5D-5L, EuroQol Group). Frequencies for each one of the subscales (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) will be presented together with the summary statistics for the total health score (ranging from 0 to 100). The number of missing responses will also be displayed. Results of the questionnaire will be also listed.

Each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). The respondent is asked to indicate his/her health state or placing a cross in the box against the most appropriate level within each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The user guide emphasises that the numerals 1-5 for each level have no arithmetic properties and should not be used as a cardinal score. Ambiguous item values (e.g., 2 levels are ticked for a single dimension) will be treated as missing values.

14 Interim Analysis

An interim analysis was planned after inclusion of 400 patients to perform a recalculation of the sample size.

However, the DSMB decided to prematurely terminate the study after inclusion of 167 patients, on 8th of December of 2021. Therefore, the interim analysis will not be performed.

15 Statistical Analyses for Safety Monitoring

A DSMB was appointed for this study. Further responsibilities and tasks were defined separately in a DSMB charter.

16 Software

If not stated otherwise, the data will be analyzed using SAS version 9.4.

17 Abbreviations

AE	Adverse Event
ANCOVA	Analysis of COVARIANCE
APACHE II	Acute Physiology And Chronic Health Evaluation II
aPTT	Activated partial thromboplastin time
AR	Adverse reaction
AT	Antithrombin
BDRM	Blind data review meeting
BE	Base excess
BGA	Blood gas analysis
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
$Ca2^{+}$	Calcium
CaO2	Arterial oxygen content
Ccr	Creatinine clearance
CI	Cardiac Index
CL^{-}	Chloride
CO2	Carbon dioxide
CP	Conditional power
eCRF	Electronic Case Report Form
CVP	Central venous pressure
DAP	Diastolic arterial blood pressure
DBL	Database lock
DO2	Oxygen delivery
DSMB	Data Safety Monitoring Board
eGFR	Estimated glomerular filtration rate
FC	Fluid challenge
Hb	Haemoglobin
HCO_3	Hydrogen carbonate
Hct	Haematocrit
HDS	Haemodynamic stability
HES	Hydroxyethyl starch
HRQoL	Health related quality of life
IA	Interim Analysis
ICU	Intensive care unit
INR	International norm ratio
IP	Investigational product
ITT	Intention to Treat
K^{+}	Potassium

KDIGO	Kidney Disease Improving Global Outcome
MANOVA	Multivariate analysis of variance
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
Na^+	Sodium
pCO_2	Partial pressure of carbon dioxide
pH	Pondus hydrogenii
pO_2	Partial pressure of oxygen
PLR	Passive leg raising
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life
RBC	Red blood cell
RRT	Renal replacement therapy
SAF	Safety analysis set
SaO_2	Arterial oxygen saturation
SAP	Statistical Analysis Plan
SAP	Systolic arterial blood pressure
SAPS II	Simplified Acute Physiology Score
SBP	Systolic blood pressure
SCr	Serum creatinine
ScvO2	Central venous oxygen saturation
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment-score
SSR	Sample size recalculation
SVI	Stroke volume index
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures

[redacted]

18 Appendices

18.1 APACHE II score

The APACHE II score will be calculated using the following criteria:

Variable	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (ºC)	>=41	39-40.9		38.5-38.9	36-38.40	34-35.9	32-33.9	30-31.9	<=29.9
Mean arterial pressure (MAP) [mmHg]	>=160	130-159	110-129		70-109		50-69		<=49
Heart rate (bpm)	>=180	140-179	110-139		70-109		55-69	40-54	<=39
Respiratory rate (bpm)	>=50	35-49		25-34	12-24	10-11	6-9		>=5
Oxygenation [mmHg] (if FiO2 >=0.5 use AaDO2, if FiO2<0.5 use PaO2)	>=500	350-499	200-349		<200 or >70 PaO2	61-70 PaO2		55-60 PaO2	<55 PaO2
Arterial PH	>=7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium [mmol/L]	>=180	160-179	155-159	150-154	130-149		120-129	111-119	<=110
Potassium [mmol/L]	>=7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine [mg/dL] Double point score for acute renal failure	>=3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Haematocrit [%]	>=60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White blood count [x10^3/mm3]	>=40		20-29.9	15-19.9	3-14.9		1-2.9		<1

Variable	0	2	3	5	6
Age (years)	<=44	45-54	55-64	65-74	>=75

Variable	5	2
Chronic health points	Nonoperative or emergency postoperative patient	Elective postoperative patient

Glasgow coma score=15-recorded score

The total APACHE II score is then calculated summing the points as specified in the tables above for each variable plus the Glasgow coma score.

If at least one variable is missing, the total APACHE II score will be missing, except for the chronic health points result that is not mandatory to fill for all patients.

18.2 SOFA score

The SOFA score is calculated using a range of points 0-4 among the distinct items:

Criteria	0	+1	+2	+3	+4
Respiratory system PaO2/FiO2 [mmHg]	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation Platelets×103/µl	≥150	<150	<100	<50	<20
Liver	<1,2	1,2–1,9	2,0–5,9	6,0–11,9	>12,0

Bilirubin (mg/dl)					
Cardiovascular system Mean arterial pressure OR administration of vasopressors required	MAP ≥70 mmHg	MAP <70 mmHg	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	dopamine 5,1-15 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min	dopamine > 15 µg/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min
Nervous system Glasgow coma scale	15	13–14	10–12	6–9	<6
Kidneys Creatinine (mg/dl)	<1,2	1,2–1,9	2,0–3,4	3,5–4,9	>5,0
Urine output (mL/d)				<500	<200

The total SOFA score is calculated by summing up the scores obtained for each one of the categories. Higher values are related to worse patient status.

If at least one criterion is missing, the total SOFA score will be missing.

18.3 SAPS II score

Criteria	26	13	12	11	9	7	6	5	4	3	2	0
Age, y												**<40**
Heart rate, beats/min				**<40**							**40-69**	**70-119**
Systolic BP, mmHg		**<70**						**70-99**				**100-199**
Body temperature, C												**<39**
Only if ventilated or continuous pulmonary artery pressure Pao2, mm Hg/Fio2				**<100**	**100-199**		**>=200**					
PaOz, kPa/Fio2				**<13.3**	**13.3-26.5**		**>=26.6**					
Urinary output, LVd				**<0.500**					**0.500-0.999**			**>=1000**
Serum urea level, mmol/L or serum urea nitrogen level, mg/dL												**<10.0 <28**
WBC count (107cu mm)			**<1.0**									**1.0-19.9**
Serum potassium, mmol/d										**<3.0**		**3.0-4.9**
Serum sodium level, mmol/L								**<125**				**125-144**
Serum bicarbonate level, mEq/L							**<15**			**15-19**		**>=20**
Bilirubin level, µ /L												**<68.4**
Glasgow Coma Score	**<6**	**6-8**				**9-10**		**11-13**				**14-15**
Chronic diseases												
Type of admission												**Scheduled surgical**

Criteria	1	2	3	4	6	7	8	9	10	12	15	17	18
Age, y						**40-59**				**60-69**	**70-74**		**>=80**
Heart rate, beats/min				**120-159**		**>=160**							
Systolic BP, mmHg		**>=200**											
Body temperature, C			**>=39**										
Only if ventilated or													

continuous pulmonary artery pressure Pao2, mm Hg/Fio2													
PaOz, kPa/Fio2													
Urinary output, LVd													
Serum urea level, mmol/L or serum urea nitrogen level, mg/dL					**10.0-29.9 28-83**				**>=30 >=84**				
WBC count (107cu mm)			**>=20**										
Serum potassium, mmol/d			**>=5.0**										
Serum sodium level, mmol/L	**>=145**												
Serum bicarbonate level, mEq/L													
Bilirubin level, µ /L				**68.4-102.5**				**>=102.6**					
Glasgow Coma Score													
Chronic diseases								**Metastatic cancer**	**Hematologic malignancy**			**AIDS**	
Type of admission					**Medical**		**Unscheduled surgical**						

The SAPS II score is made up of 17 variables: 12 physiological variables, age, type of admission (scheduled surgical, unscheduled surgical, or medical), and three variables related to underlying disease: acquired immunodeficiency syndrome, metastatic cancer, and hematologic malignancy. Points assigned for each variable vary from 0 to 3 (for temperature) up to 0 to 26 (for Glasgow Coma Score).

For the 12 physiological variables, the worst value during the first 24 hours in the ICU is taken into account.

No arterial sample is necessary if the patient is not ventilated or receiving continuous positive airway pressure.

For sedated patients, the Glasgow Coma Score before sedation was used. This was ascertained either from interviewing the physician who ordered the sedation, or by reviewing the patient's medical record.

The total SAPS score is calculated by summing up the scores obtained for each one of the categories. Higher values are related to worse patient status.

If at least one criterion is missing, the total SAPS II score will be missing.

18.4 KDIGO score

Stages will be derived based on the following values of serum creatinine:

Stage	Serum creatinine
1	1.5–1.9 times baseline OR ≥ 0.3 mg/dl (≥ 26.5 mmol/l) increase
2	2.0–2.9 times baseline
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl (≥ 353.6 mmol/l) OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m2

For calculating baseline KDIGO scores, the simplified 'modification of diet in renal disease' (MDRD) formula provides a robust estimate of GFR relative to serum creatinine based on age, race and sex.

Therefore, the recorded serum creatinine value at baseline visit will be compared using the KDIGO scoring table with the estimated value following this formula. The following protocol table establishes the estimated baseline creatinine that will be used for comparison using:

Age (years)	Black males mg/dl (umol/l)	Other males mg/dL (umol/l)	Black females mg/dl (umol/l)	Other females mg/dl (umol/l)
20-24	1.5 (133)	1.3 (115)	1.2 (106)	1.0 (88)
25-29	1.5 (133)	1.2 (106)	1.1 (97)	1.0 (88)
30-39	1.4 (124)	1.2 (106)	1.1 (97)	0.9 (80)
40-54	1.3 (115)	1.1 (97)	1.0 (88)	0.9 (80)
55-65	1.3 (115)	1.1 (97)	1.0 (88)	0.8 (71)
>65	1.2 (106)	1.0 (88)	0.9 (80)	0.8 (71)

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