CReep and maintenance flUid Sodium chloride ADministration rEduction in cRitically ill adultS

The CRUSADERS randomized controlled trial

SAlt baLAnce Detailed INsight – nested substudy

The SALADIN nested substudy

PROTOCOL VERSION **1.1** RELEASED ON **25 MAY 2025**

RESEARCH REFERENCE NUMBERS

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators agree to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in " CTR 536/2014", and any subsequent amendments, GCP guidelines and, the Belgian law of May 7th 2017 regarding clinical trials with IMP, the Sponsor's SOPs, and other regulatory requirements as amended.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

*** RESEARCH PARTICIPANT INFORMATION REMOVED AS PER CLINICALTRIALS.GOV INSTRUCTIONS ***

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KEY STUDY CONTACTS

*** RESEARCH PARTICIPANT INFORMATION REMOVED AS PER CLINICALTRIALS.GOV INSTRUCTIONS ***

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Funder(s)	
Clinical Trials Unit (CTU)	
Statistician	
Data Manager	
Committees	-
DPO	
Ombudsman Service Sponsor	
Monitor(s)	
Add any relevant member not listed above	

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
(e)CRF	(electronic) Case Report Form
(e)ISF	(electronic) Investigator Site File
(e)TMF	(electronic) Trial Master File
ADH	AntiDiuretic Hormone
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ARDS	Acute Respiratory Distress Syndrome
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CI	Chief Investigator
Co-CI	Co-Chief Investigator
CPAP	Continuous Positive Airway Pressure
CTA	Clinical Trial Authorisation
CTIS	Clinical Trial Information system
CTMS	Clinical Trial Management System
CTR	Clinical Trial Regulation
CTC	Clinical Trial Center
CTU	Clinical Trial Unit
DAOH	Days Alive and Out of Hospital
DAWOLS	Days Alive and WithOut Life Support
DSMB	Data and Safety Monitoring Board
DPO	Data Protection Officer
EC	Ethics Committee
ECW	Extracellular Water
ECG	Electrocardiogram
EFWC	Electrolyte-free water clearance
eGFR	Estimated Glomerular Filtration Rate
ER	Emergency Room
EudraCT	European Clinical trials Database
EudraVIGILANCE	European database for Pharmacovigilance
EVF	Extravascular Fluid
FFM	Fat-Free Mass
FFMH	Fat-Free Mass Hydration
FM	Fat Mass
FPI	First Participant In
FWC	Solute-free water clearance
FWO	Research Foundation Flanders (Fonds voor Wetenschappelijk Onderzoek)
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GMP	Good Manufacturing Practices
HEFrEF	Heart failure with reduced ejection fraction
HFNC	High Flow Nasal Canula

ICH	International Council on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ICU	Intensive Care Unit
ICW	Intracellular Water
IHD	Intermittent hemodialysis
IMP	Investigational Medicinal Product
IQR	Interquartile Range
ISE	Ion-Selective Electrode
IV	Intravenous
IVF	Intravascular Fluid
KDIGO	Kidney Disease Improving Global Outcomes
LOS	Length Of Stay
LVEF	Left Ventricular Ejection Fraction
MAP	Mean Arterial Pressure
MS	Member State
NRS	Numeric Rating Scale
OR	Operating Room
P/F ratio	PaO2 over FiO2 ratio
PI	Principal Investigator
PM	Project Manager
POCT	Point Of Care Test
PPI	Patient and Public Involvement
RASS	Richmond Analgesia and Sedation Scale
RCT	Randomized Controlled Trial
RMR	Resting Metabolic Rate
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SIADH	Syndrome of Inappropriate ADH Secretion
SAR	Serious Adverse Reaction
SC	Study Coordinator
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMS-ICU	Simplified Mortality Score for the Intensive Care Unit
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBSA	Total Body Surface Area
TBW	Total Body Water
TMG	Trial Management Group
TSC	Trial Steering Committee
UZA	Universitair Ziekenhuis Antwerpen (Antwerp University Hospital)
VE	Volume Excess
WOCBP	Women of Childbearing Potential
ZAS	Ziekenhuis aan de Stroom (ZAS Network of Hospitals)

VERSION HISTORY LOG

DOCUMENT HISTORY		
VERSION NUMBER	**DATE** (DDMMMYYYY)	**SECTIONS THAT HAVE BEEN ADAPTED (WITH SHORT DESCRIPTION AND NAME OF THE PERSON WHO MADE THE ADAPTATIONS)**
0.9	05 DEC 2024	Initial version after FWO-TBM funding approval
0.91	05 JAN 2024	Version after first input by CTC and statistician, finetuning by CI – changes throughout made by ***
0.92	12 JAN 2025	Next iteration after input statistician and CTC – changes throughout made by ***
0.93	19 JAN 2025	Next iteration after input statistician and CTC – changes throughout made by ***
0.94	25 JAN 2025	Prefinalization before TSC – changes throughout made by ***
0.99	11 FEB 2025	Prefinalization after input of TSC – changes as discussed in the TSC meeting minutes – adaptations made by ***
1.0	05 MAR 2025	Final Protocol pre submission to CTIS – finetuning and removing comments – adaptations made by ***
1.1	25 MAY 2025	Implementation of comments made by CTIS reviewers (adding WOCBP policy, Study Flowchart, adding stratification variables, statistical finetuning – adaptations made by ***

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STUDY SUMMARY

Study Title	**Effect of Reduced Sodium Chloride in Fluid Creep and Maintenance Fluids in Critically Ill Adults: A Randomized Controlled Trial**
Short Title	**CReep and maintenance flUid Salt Administration rEduction in cRitically ill adultS (CRUSADERS)** SAlt BaLAnce Detailed INsight (SALADIN) nested substudy
Lay Title (in dutch)	**Studie naar het effect van een verminderde zouttoediening via infuusvloeistoffen bij ernstig zieke volwassenen op Intensieve Zorg**
Internal reference (if applicable)/ CTMS number	003813
EUCT Number	2025-520744-14-00
Study Design	Multi-center, prospective, randomized, double-blind phase IV low-intervention trial. Primary and all safety outcomes will be analyzed according to the intention-to-treat principle of all randomized patients with obtained informed consent.
Study Participants and setting	Inclusion criteria 1. At least 18 years of age 2. Patients who are admitted to the ICU for medical or surgical emergencies, including complications of elective surgery 3. The treating physician expects the patient will still require ICU care in two days, indicating a severe or complex condition at enrollment 4. The patient is expected to receive at least 300 mL of fluid creep or at least 1L of maintenance fluid according to study arm during the first 24h after inclusion. Exclusion criteria 1. A contraindication to hypotonic fluids due to risk of brain edema 2. Hyponatremia below 131 mmol/L at admission 3. Admission solely for treatment of fluid accumulation due to cardiac decompensation, without other acute medical conditions requiring ICU-level care. 4. Patient's death is deemed imminent and inevitable, admission for palliative care or admission solely for organ donation 5. Patient receiving chronic renal replacement therapy 6. Patients referred after a stay of more than 24 hours in another ICU 7. Patients randomized in CRUSADERS before 8. Patient is co-enrolled in an unapproved concomitant ICU-trial or in any trial with an intervention that affects fluid administration or fluid balance. Additional exclusion criteria for participation in SALADIN nested substudy 1. Expected to require renal replacement therapy within 24 hours 2. Increased insensible fluid losses: burns, extensive wounds or skin defects or massive diarrhea,… 3. No urinary catheter in place 4. Expected to require bladder irrigation within 24 hours 5. Chronic treatment with loop or thiazide diuretics The trial is conducted in four mixed ICUs of varying sizes across Belgium.
Intervention(s) **- IMP Formulation, Dose, Route of Administration of IMP**	Sodium-chloride reduction strategy: **NaCl-poor arm** Fluid creep: - Medications, including concentrated electrolytes, are dissolved in **glucose 5%** except when another solvent is mandatory - Infusions for *intravenous* line patency are **glucose 5%**. Maintenance fluids: - Type: maintenance fluid is **NaCl 0.3% in glucose 3.3%**

	- Rate and indication: at the discretion of the treating physician, typically 25-30 ml/kg of body weight with a maximum of 100 ml/hour, accounting for concomitant fluid sources such as nutrition and fluid creep. It is allowed to prescribe a higher volume of study maintenance fluids to include replacement.	
Control	Standard, isotonic fluid arm: **NaCl-rich arm** Fluid creep: - Medications, including concentrated electrolytes, are dissolved in **NaCl 0.9%** except when another solvent is mandatory - Infusions for line patency are **NaCl 0.9%**. Maintenance fluids: - Type: Maintenance fluid is **PlasmaLyte**. - Rate and indication: at the discretion of the treating physician, typically 25-30 ml/kg of body weight with a maximum of 100 ml/hour, accounting for concomitant fluid sources such as nutrition and fluid creep. It is allowed to prescribe a higher volume of study maintenance fluids to include replacement.	
	Objectives	**Outcome Measures**
Primary	To evaluate the effect of the intervention on mortality and life support (mechanical ventilation and renal replacement therapy, but excluding vasopressor use)	Days alive and without life support (DAWOLS) at 90 days after ICU admission
Secondary	Safety endpoints: to evaluate the effect of the intervention on - Sodium and chloride disorders - Fluid retention - Glycemic disorders - Acute kidney injury and need for renal replacement therapy - Need for mechanical ventilation - ICU and hospital mortality - ICU and hospital length of stay Efficacy endpoints: to evaluate the effect on - Daily and total cumulative sodium, chloride and glucose administration, within and outside the intervention. - Daily and total cumulative fluid balance (excluding insensible losses) with and without diuretics/renal replacement therapy	Safety endpoints: - Occurrence of moderate and severe hyponatremia, moderate and severe hypernatremia and moderate and severe hyperchloremia (number of patients with at least one event). - Time between randomization and the first administration of an IV loop diuretic - Proportion of ICU days during which IV loop diuretics were administered - Cumulative fluid balance from ICU admission to the morning of the first ICU day on which an IV loop diuretic is prescribed - Proportion of glucose assessments with glycemia >180 mg/dL relative to the total number of assessments - Mean daily glycemia for each ICU day - Occurrence of hypoglycemia < 70 mg/dL (number of patients with at least one event). - Occurrence of new-onset AKI (KDIGO stage 2 or 3) from the third ICU day after randomization (number of patients with at least one event) - Days without renal replacement therapy at D90 - New-onset need for RRT from the second ICU day after randomization - Ventilator-free days at D90 - New-onset need for mechanical ventilation from the second ICU day after randomization - Days alive and out of hospital at D90 of admission

		- ICU and hospital mortality at D90 of admission - ICU and hospital length of stay Efficacy endpoints: - Daily and total cumulative sodium, chloride and glucose administration due to study and non-study fluids - Daily and total cumulative fluid balance (excluding insensible losses), separately for days with and without IV loop diuretics or RRT
Exploratory	To evaluate salt-induced catabolism and muscle wasting by assessing serum urea-to-creatinine ratio **SALADIN nested substudy** - To determine daily cumulative sodium and chloride balance (administered minus urine excretion) and correlate with daily cumulative fluid balance, free water clearance, bioelectrical impedance analysis, volume kinetics analysis and body weight	Difference in the serum urea-to-creatinine ratio measured every other ICU Day in patients not receiving RRT **SALADIN nested substudy** - Daily and cumulative sodium and chloride administration (study fluids, non-study fluids excl. non-study fluid creep, nutrition excl. oral intake) minus urine sodium and chloride on 24h urine collections - Solute-free and electrolyte-free water clearance - Volume kinetics assessments - Bioelectrical impedance analysis assessments - Measured body weight
Planned Sample Size	640	
Recruitment period	Estimated recruitment period 2.5 years Estimated trial start: Q3 2025 (First patient, First visit) Estimated trial end: Q1 2028 (Last patient, Last visit)	
Treatment duration	During the patient's ICU stay: - eligible patients are randomized before the patient's ICU stay reaches the second 12:00 noon - the treatment phase begins immediately after randomization and continues until the patient is discharged from the ICU or until the study-specific fluid is no longer available in the department as per the randomization schedule (at least 28 days after randomization). - in the case of readmission to the ICU, the patient continues to receive study fluids according to the study arm if study fluid is still available in the department.	
Follow up duration	90 days after ICU admission	
Duration of the study	4 years	

STUDY SCHEDULE OF ASSESSMENTS - FLOWCHART

*Table 1: Schedule of assessments, standard-of-care procedures are marked with **

	Screening, enrollment and randomization	*Baseline Assessments*	*Treatment Phase (each ICU Day, from randomization to ICU discharge, including readmissions)*	*Follow up Phase*	*End of study visit* *Day 90 after ICU admission (follow up phone call if post-discharge)*
Acceptable windows	*Randomization must be completed before the patient's ICU stay reaches the second 12:00 noon (See Figure 1)*		*None*	*N/A*	*+10 Days*
Eligibility assessment	*X*[(1)]				
Informed consent	*X*[(2)]				
Randomization	*X*[(3)]				
Demographic data, including medical history		*X*			
ICU admission data including severity and organ failure scoring		*X*			
Estimated body weight, body height and BMI*		*X*			
Lab assessments (serum Na (ISE and		*X*	*X*		

POCT), CI (ISE and POCT), albumin and creatinine)*					
Serum urea (every other ICU day)			*X*[14]		
Glycemia levels (blood gas analyzer)*		*X*	*X*		
Detailed fluid balance (input – output) over past ICU day*			*X*[4]		
Recording administration of IV loop diuretics[5]		*X*	*X*		
New-onset AKI, including baseline creatinine			*X*		
Mechanical ventilation: invasive and noninvasive ventilation and CPAP		*X*	*X*	*X*[6]	*X*[6]
Renal replacement therapy[7]		*X*	*X*	*X*[6]	*X*[6]
SUSARs and predefined SARs		*X*	*X*	*X*	
ICU length of stay					*X*[6]
Survival status or destination at ICU discharge[8]					*X*

Hospital length of stay[9]					*X*
Survival status or destination at hospital discharge[9]					*X*
Ventilation-free days[6]					*X*
Renal replacement therapy-free days[7]					*X*
Days alive and without life support					*X*
Days alive and out of hospital[9]					*X*
Additional assessments for SALADIN nested substudy					
Additional SALADIN exclusion criteria[12]	*X[13]*				
Additional study assessments: volume and type of IV fluids in 24h before ICU admission, concomitant diuretics		*X*	*X*		
24h urine collection biochemistry assessments, including calculations of free water clearance (incl. plasma osmolality on morning routine blood sample*)			*X*[10]		

Volume kinetics calculations (using whole blood hemoglobin and serum sodium*)		*X*	*X*		
Bioelectrical Impedance Analysis(11)		*X*	*X*		
Measured body weight		*X*	*X*		

(1) To confirm elegibility, the following parameters are needed: age, admission type, medical neurological contraindication, sodium level, chronic RRT status, concomitant trials or previous enrollment in CRUSADERS. For enrollment in SALADIN nested substudy, additional exclusion criteria should be checked, for details see (12).

(2) See 1.8.2. Informed consent procedure. If patient is competent, or legal representative is present and situation allows for detailed discussion: written informed consent is obtained before Randomization. If patient is incompetent, awaiting legal representative or awaiting possibility of detailed discussion: deferred consent procedure.

(3) Randomization only after eligibility is confirmed.

(4) Fluid balance data are collected up to the morning of the day of ICU discharge

(5) Precise time of first administration of an IV loop diuretic is recorded, later defined as use of IV loop diuretic throughout the ICU day.

(6) Including ICU Days after discharge to another ICU

(7) Up to three days between sessions of intermittent hemodialysis are counted as days with RRT.

(8) If patient is discharged to another ICU, these ICU days are counted within the length of stay in the original ICU

(9) If a patient is transferred to another hospital, the additional days spent in that hospital are included in the total hospital length of stay for the study endpoint, but revalidation wards are excluded.

(10) Collected until the ICU day on which bladder catheter removal, initiation of bladder irrigation, start of renal replacement therapy, or ICU discharge occurs, whichever comes first. Additional exclusion criteria: RRT or increased insensible losses.

(11) To be conducted at least once every three ICU days starting from the day of randomization.

(12) For enrollment in SALADIN nested substudy, it should be verified that the patient is not expected to receive RRT in the first 24h hours, has no sources of increased insensible losses, is not under concomitant treatment with loop or thiazide diuretics, does not need bladder irrigation and has a urinary catheter in place.

(13) Patients who participate in the SALADIN nested substudy need to be randomized before the first urine is dismissed (usually at the end of the first ICU Day).

(14) From the ICU day after randomization, until ICU discharge or the start of RRT, whichever comes first.

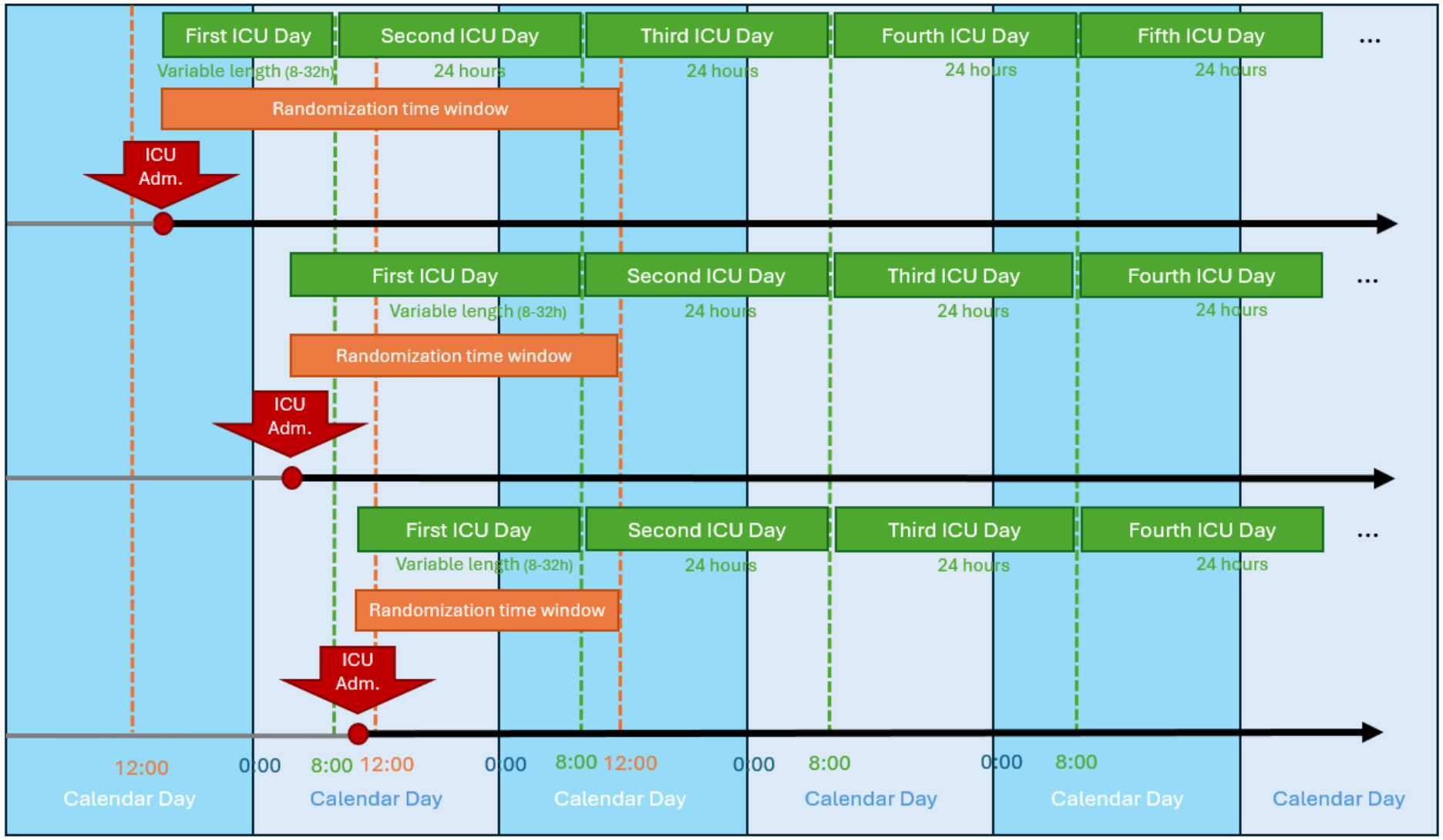
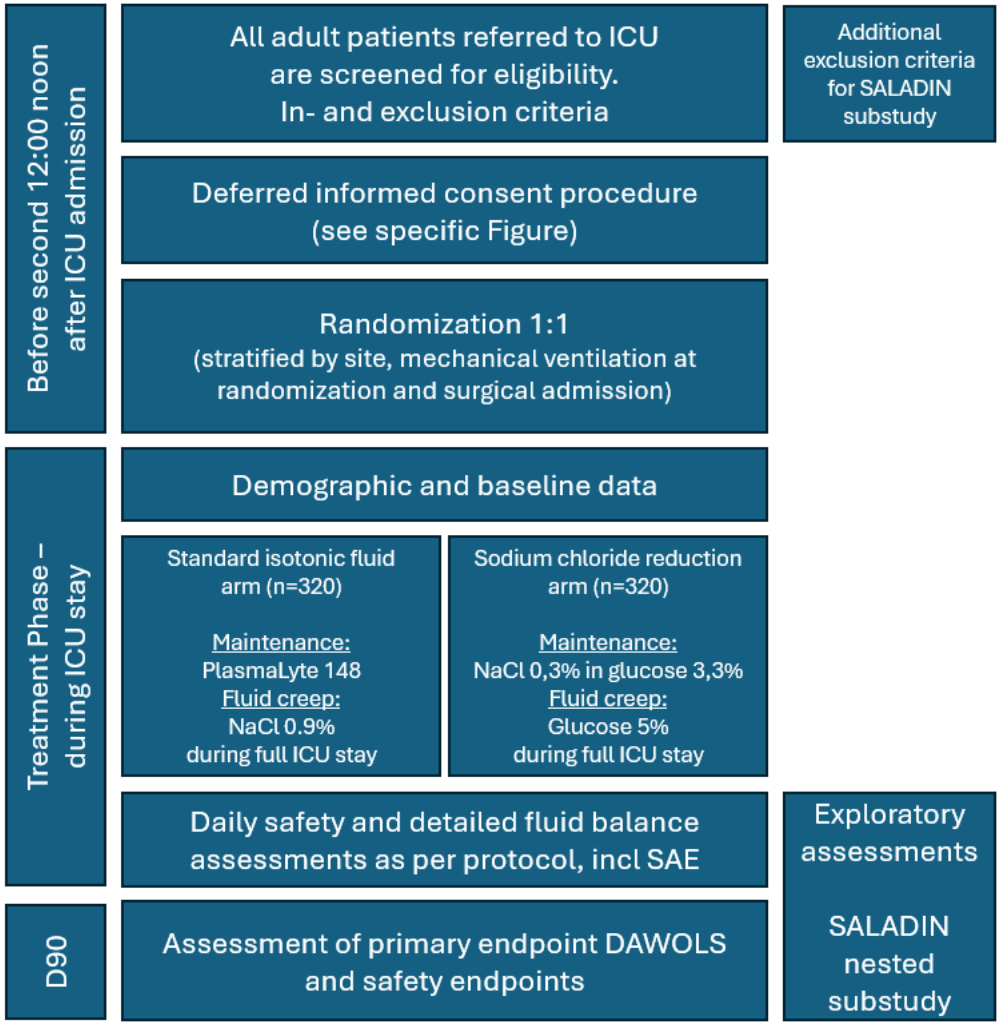


Figure 1: Overview of the definition of ICU days and the randomization time window, depending on the time of ICU admission. The first ICU Day spans from admission to 8AM the following calendar day; subsequent ICU days run from 8 AM to 8 AM the following calendar day; the day of ICU discharge runs from 8AM to the moment of discharge. Eligible patients are to be randomized before the patient's ICU stay reaches the second 12:00 noon.

TRIAL FLOWCHART



1. STUDY PROTOCOL

1.1 BACKGROUND

Large amounts of sodium and chloride under the form of intravenous fluids are daily administered to hospitalized patients in hospitals worldwide, and even more so in the ICU.(1) It is known from experimental and clinical data that the kidneys inefficiently excrete sodium chloride burdens that exceed normal dietary intake.(2-4) This has two important consequences:

First, sodium burdens lead to **fluid retention**. Various scientific evidence supports the impact of fluid accumulation and fluid overload on mortality and morbidity in critical care settings.(5-7) Numerous studies have investigated the relationship between fluid balance and patient outcomes, providing valuable insights into the consequences of fluid management strategies in critically ill individuals:

- Association with **mortality**: several observational studies and meta-analyses have demonstrated a significant association between positive fluid balance or fluid overload and increased mortality in critically ill patients.(8-10)
- Impact on **respiratory function**: research has shown that fluid overload contributes to the development of pulmonary edema and worsens respiratory function in critically ill patients.(5) A study published in the New England Journal of Medicine in 2006 reported that conservative fluid management strategies were associated with improved lung function and reduced mortality in patients with acute lung injury.(11) A conservative or deresuscitative fluid strategy was demonstrated to result in an increased number of ventilator-free days and a decreased length of ICU stay compared with a liberal strategy or standard care.(12)
- **Renal dysfunction and AKI**: Multiple studies have demonstrated that fluid overload is a risk factor for the development and progression of acute kidney injury (AKI) in critically ill patients.(13)
- **Other clinically relevant outcomes**: Research has also demonstrated that fluid overload is associated with worse clinical outcomes in critically ill patients, including longer duration of mechanical ventilation, increased length of stay in the intensive care unit (ICU), and higher rates of complications such as infections and organ failure.

Second, chloride burdens lead to **hyperchloremia**. This electrolyte disturbance has several consequences in the intensive care unit (ICU):

- **Renal dysfunction**: Hyperchloremia has been associated with acute kidney injury (AKI) and impaired renal function in ICU patients. Elevated chloride levels can alter renal perfusion and tubular function, contributing to the development or progression of AKI.(14, 15)
- **Increased mortality**: A 2024 meta-analysis concluded that the estimated effect of using chloride-poor balanced solutions versus NaCl 0.9% in critically ill adult patients had a 90% probability of slightly reducing mortality.(16)

Up till now, almost all prior fluid research efforts went into resuscitation fluids. The focus of this research was on (a) reducing volumes to limit fluid balance, which is very challenging and calls for expensive hemodynamic monitoring techniques and could lead to patients receiving insufficient fluid and (b) reducing chloride burdens by the use of chloride-poor alternatives to normal saline. Substantial scientific (and thus intellectual and financial) efforts went into this research and it is now believed that fluid volume restriction beyond a rational standard-of-care has little added value (CLASSIC trial, CLOVERS trial) and that a chloride-poor strategy has a high probability to slightly reduce mortality.(16-18)

The large number of patients to demonstrate the harm of NaCl 0.9% is at least partially explained by the fact that resuscitation fluids are responsible for **only 6% of the total amount of fluids** (Figure 2) and that **potential to reduce their sodium and chloride content is limited** as resuscitation fluids need to be isotonic to plasma. In the large trials, studying balanced versus unbalanced solutions a mere two to three liters of study fluid were administered during ICU stay, mostly in the first days of admission and had a chloride difference of 56 mmol/L (154 mmol/L for NaCl 0.9% versus 98 mmol/L for PlasmaLyte) (Figure 3).

Figure 2: Distribution of the different mean daily fluid volumes (average of 14,654 patients on their cumulative 103,098 days of ICU stay) in a ten-year period (2007-2016) in the intensive care department of Antwerp University Hospital. Not all fluid creep can be manipulated as some medications are predissolved. In this study, it was impossible to distinguish maintenance from replacement fluids.

1.2 RATIONALE

It is perfectly possible to avoid most of these sodium chloride burdens easily and at almost no cost, by dealing with **two other important sources** of sodium and chloride administration in the hospital.(1, 2)

First, **fluid creep, the large volume of fluid that is administered to patients to dissolve intravenous medication and to keep intravenous lines open**. Our and other groups demonstrated that fluid creep accounts to more than 30% of the fluid volume that is administered to patients in the ICU.(19, 20) Prior literature showed that changing creep fluids to sodium-free alternatives is associated with a lower incidence of hyperchloremia, possible acute kidney failure and a lower fluid balance (21, 22), but the effect on hard clinical outcomes has never been researched as the primary endpoint so that the current state-of-the-art is largely based on local custom and personal belief. Due to a lack of evidence, and because the issue did not get much attention, by far the most medications are still being dissolved in NaCl 0.9%.

The second most important source of sodium are **maintenance solutions that are prescribed to cover patients' daily needs for water and electrolytes in patients that are unable to ingest food or fluids.** Maintenance and replacement fluids (the latter are not the subject of our intervention) are responsible for about 25% of fluid administration (Fig 2).(1) The few guidelines that are available are from the UK and recommend sodium-poor maintenance fluids in hospitalized adults. Yet, surveys learn that this strategy is very rarely adopted outside England. Some authors also openly critique the guidelines out of fear for an increased incidence of hyponatremia.(23) Our group showed the effect size of a hypotonic compared to isotonic maintenance fluids on fluid balance in healthy volunteers (600mL in 28h) and in the perioperative setting after major thoracic surgery (1.4L in 72h).(3, 4, 24) Both studies demonstrated a clinically relevant fluid retention in the sodium and chloride-rich intervention arms. The studies were underpowered to demonstrate hard clinical outcomes, although in the surgical patients, the sodium-rich treatment needed to be stopped in more patients due to clinically relevant fluid overload (p=0.06) and no more severe hyponatremia was observed. The transition from healthy persons to the perioperative situation demonstrates that as the amount of salt administration increases, the significance of fluid retention also increases. Additionally, the presence of a sodium-retaining condition, such as general anesthesia, dramatically amplifies this effect. Therefore, the **next logical step is to expand this area of research to the critically ill patient**, who experiences **even higher levels of salt exposure for an extended period of time, as well as increased sodium retention caused by hypovolemia and capillary leakage**, compared to the surgical environment.

Dealing with both of these fluid sources can be seen as picking low-hanging fruit, especially since the intervention comes at no additional cost. First, the intervention will affect fluid balance and fluid accumulation without intervening in the administered volume, but by a reduction in sodium and chloride

administration. Second, it is easy to appreciate that targeting maintenance fluids and fluid creep will reduce chloride burdens much more than can ever be possible by changing resuscitation strategies (Figure 3). Despite the fact that an unfavourable signal/noise ratio is inherent to all the trials investigating the effect of fluid composition on patient-centered outcomes, the chance of demonstrating a clinically relevant effect is much higher than when targeting resuscitation fluids. **Reducing salt administration to critically ill patients is an easy and costless intervention, with a high preventive potential, enabling a foundation for a rapid and broad change in clinical practice at hospital and patient level.** Adopting a sodium-poor maintenance strategy and dissolving medication in a sodium-free fluid are both effective measures to accomplish this goal.

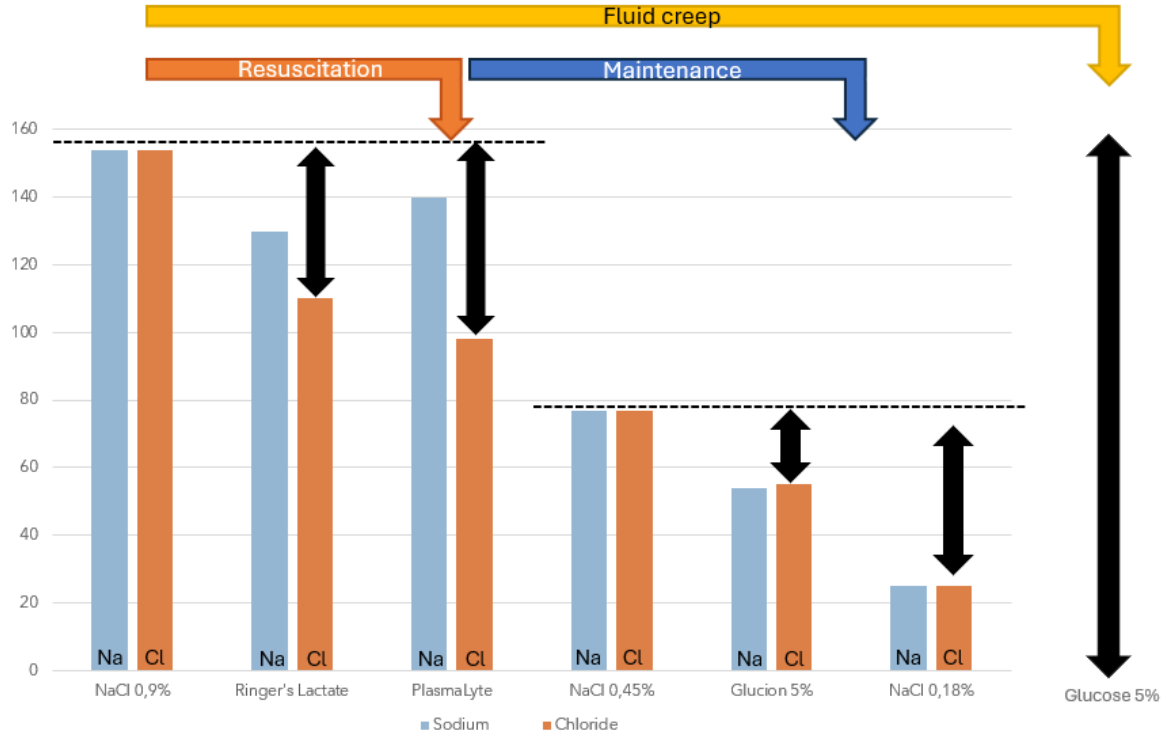


Figure 3: Change in composition of fluid due to the study intervention as compared to changing resuscitation fluids from NaCl 0.9% to balanced solutions, to illustrate the impact on salt burdens that will be achieved in the intervention arm.

A **potential drawback of reducing salt administration** is the occurrence of **hyponatremia**, which might be an independent contributor to worse outcomes. Indeed, more free water and less sodium will be administered to patients who might retain more free water than healthy individuals.(23) This could lead to an increased incidence of delirium.(25) This is the main reason why guidelines to use hypotonic maintenance fluids are often not followed.(26) This could especially be the case in patients with occult hypovolemia, leading to the secretion of vasopressin. Another consequence of reducing sodium chloride is that more glucose-containing fluids will be administered. Another consequence of reducing sodium chloride intake is the increased administration of glucose-containing fluids, which may lead to **hyperglycemia**. While hyperglycemia is generally well-controlled in the ICU setting, it has been linked to worse clinical outcomes.(27)

1.3 ASSESSMENT AND MANAGEMENT OF RISK

This study can be categorized as a **phase IV, low-intervention** clinical study.

→ Rationale to classify the study as low-intervention:

- The study fluids for intravenous administration are authorised, used in accordance with the terms of marketing authorisation, and both study regimens (control and intervention) are currently used as the local standard of care in different hospitals in Belgium and throughout the world. In many cases, this particular choice is even not well-considered or the consequence of local habits.
- All medicinal products involved have been used daily and globally in hospitals for decades.

- The additional diagnostic or monitoring procedures are largely within the routine standard-of-care and do not pose any additional risk or burden to the safety of the subjects compared to normal clinical practice. The only additional serum assessment is the measurement of urea, which is performed on blood samples obtained as part of routine care. In the SALADIN nested substudy, the only additional procedures are the daily collection of urine output for biochemical analysis, measuring body weight and bioelectrical impedance analysis, a strictly harmless procedure.
- The CRUSADERS trial will be conducted in an ICU setting where patients receive continuous, round-the-clock monitoring and care from ICU nurses and doctors trained to manage all potential consequences associated with the interventions being used. This comprehensive level of care ensures the safety of individual patients enrolled in the trial.

1.4 OBJECTIVES AND ENDPOINTS / OUTCOME MEASURES

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adults by targeting the sodium and chloride content of fluid creep and maintenance fluids will improve patient-important outcomes in critically ill adults.

1.4.1 Primary objective

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adult patients by targeting the sodium and chloride content of fluid creep and maintenance fluids leads to a better outcome in terms of **mortality and respiratory and renal organ support**, compared to a regimen in which fluid creep and maintenance fluids predominantly consist of isotonic solutions.

1.4.2 Secondary objectives

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adult patients by targeting the sodium and chloride content of fluid creep and maintenance fluids is non-inferior to a regimen in which fluid creep and maintenance fluids predominantly consist of isotonic solutions in terms of the incidence of **moderate and severe hyponatremia with a non-inferiority margin for severe hyponatremia (< 125 mmol/L) of 5%, and in the incidence of hyperglycemia**. Additionally, we hypothesize the intervention will result in a lower incidence of **moderate and severe hypernatremia, hyperchloremia and hypoglycemia**.

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adult patients by targeting the sodium and chloride content of fluid creep and maintenance fluids will result in a **lower cumulative fluid balance before administration of IV loop diuretics and a delayed and reduced need for IV loop diuretics to manage fluid retention**, compared to a regimen in which fluid creep and maintenance fluids predominantly consist of isotonic solutions.

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adult patients by targeting the sodium and chloride content of fluid creep and maintenance fluids will result in **lower incidence of acute kidney injury, a lower new-onset need for renal replacement therapy and a shorter duration renal replacement therapy,** compared to a regimen in which fluid creep and maintenance fluids predominantly consist of isotonic solutions.

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adult patients by targeting the sodium and chloride content of fluid creep and maintenance fluids will result in **a lower new-onset need for mechanical ventilation and a shorter duration of mechanical ventilation,** compared to a regimen in which fluid creep and maintenance fluids predominantly consist of isotonic solutions.

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adult patients by targeting the sodium and chloride content of fluid creep and maintenance fluids will result in **a reduced ICU and hospital mortality and shorter ICU and hospital lengths of stay**, compared to a regimen in which fluid creep and maintenance fluids predominantly consist of isotonic solutions.

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adult patients by targeting the sodium and chloride content of fluid creep and maintenance fluids will result in **substantially lower sodium and chloride burdens and subsequently lower cumulative fluid balances**, compared to a regimen in which fluid creep and maintenance fluids predominantly consist of isotonic solutions.

1.4.3 Exploratory objectives

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adult patients by targeting the sodium and chloride content of fluid creep and maintenance fluids will result in **a lower level of catabolism and muscle wasting**, compared to a regimen in which fluid creep and maintenance fluids predominantly consist of isotonic solutions.

A nested substudy **SALADIN** (**SA**lt ba**LA**nce **D**etailed **IN**sight) in a targeted 150 patients investigates detailed sodium and chloride balances. Patients in the SALADIN nested substudy will undergo daily urine collections, volume kinetics calculations and bioelectrical impedance analysis and measurements of body weight leading to important additional physiological insights.

We hypothesize that a strategy of reducing the sodium chloride burdens in critically ill adult patients by targeting the sodium and chloride content of fluid creep and maintenance fluids will result in **lower sodium and chloride balances**, compared to a regimen in which fluid creep and maintenance fluids predominantly consist of isotonic solutions. Findings will be correlated with **cumulative fluid balance, solute- and electrolyte-free water clearance, assessments of volume kinetics, bioelectrical impedance analysis and measured body weight**.(28, 29)

1.4.4 Primary endpoint

The primary endpoint of the CRUSADERS study is **Days alive and without life support (DAWOLS) at 90 days after ICU admission**.

- Mortality is penalized and receives a value of DAWOLS of zero and is determined at day 90 after ICU admission.
- Mechanical ventilation is defined as invasive or non-invasive ventilation (CPAP or with any amount of pressure or volume support but excluding high-flow nasal oxygen). On each ICU Day (Figure 1), the presence of mechanical ventilation is counted when this type of support has been in place. The days following extubation are only counted as ventilator-free days when no re-intubation happens within 48 hours of extubation.
- Renal replacement therapy (RRT) is defined as the use of continuous renal replacement therapy, peritoneal dialysis or intermittent hemodialysis (IHD). The presence of continuous renal replacement therapy is counted when this type of support has been in place during an ICU Day. Periods with up to 3 days between IHD are counted as days with RRT, e.g. if a patient received IHD on day 1, did not receive IHD on days 2–4, and received IHD again on day 5, the patient is considered to have been on RRT for the entire period from day 1 through day 5.
- Vasopressor use is not considered as life support. The exclusion of vasopressor use as a relevant form of life support in this study is based on several factors: the progressively lower threshold for initiation by clinicians, the subjectivity in defining a clinically relevant dose, the continued administration in cases where it may no longer be strictly necessary, and its lower clinical relevance compared to mechanical ventilation and renal replacement therapy

→ Rationale: The choice of the primary endpoint in large ICU trials is notoriously challenging, as mortality alone depends on a large number of factors, that are more often than not unrelated to a single intervention. According to patient questionnaires, there are also outcomes “worse than death”. The choice of a “softer” endpoints, such as electrolyte disorders or the early stages of kidney failure provide only circumstantial evidence of true harm. Moreover, the intervention could be characterized by a beneficial effect on different organ systems, such as the duration of mechanical ventilation (due to fluid overload) and the avoidance of renal replacement therapy (due to fluid overload and hyperchloremia). DAWOLS is an endpoint that is deemed relevant, by clinicians and patients alike, as being discharged home and weaned off life support is relevant to quality of life.(30, 31).

1.4.5 Secondary endpoints

1.4.5.1 Safety endpoints

- **Occurrence of moderate and severe hyponatremia**

Moderate hyponatremia is defined as 125-129 mmol/L and severe as <125 mmol/L analyzed as the number of patients with at least one instance of the disturbance.(32)

Each ICU day, routine morning sodium assessment is collected, without its specific timestamp.

To be considered as an instance of hyponatremia, there has to be a sodium level decrease of at least 3 mmol/L compared to the baseline level to account for mild hyponatremia at baseline and for analytical errors.

The electrolyte levels used for this endpoint are the measurements analyzed in the central lab (ion-specific electrode or ISE). Serum albumine levels, if available on the same blood sample and point-of-care sodium assessments from the blood gas analyzer, performed within 2 hours of the ISE analysis, are recorded to cross-check and to assess potential interference in a sensitivity analysis.

→ Rationale: the NaCl-poor arm could be associated with a higher occurrence of hyponatremia as more free water is administered and critically ill patients sometimes experience increased levels of antidiuretic hormone.(23)

- **Occurrence of moderate and severe hypernatremia**

Moderate hypernatremia is defined as 151-155 mmol/L and severe as >155 mmol/L analyzed as the number of patients with at least one instance of the disturbance.

Each ICU day, routine morning sodium assessment is collected, without its specific timestamp.

To be considered as an instance of hypernatremia, there has to be a sodium level increase of at least 3 mmol/L compared to the baseline level to account for mild hypernatremia at baseline and for analytical errors.

The electrolyte levels used for this endpoint are all the measurements analyzed in the central lab (ion-specific electrode or ISE). Serum albumine levels, if available on the same blood sample and point-of-care sodium assessments from the blood gas analyzer, performed within 2 hours of the ISE analysis, are recorded to cross-check and to assess potential interference in a sensitivity analysis.

→ Rationale: the NaCl-rich arm could be associated with a higher occurrence of hypernatremia.(4)

- **Occurrence of moderate and severe hyperchloremia**

Moderate hyperchloremia is defined as 111-115 mmol/L and severe as >115 mmol/L analyzed as the number of patients with at least one instance of the disturbance.

Each ICU day, routine morning chloride assessment is collected, without their specific timestamp.

To be considered as an instance of hyperchloremia, there has to be a chloride level increase of at least 2 mmol/L compared to the baseline level to account for mild hyperchloremia at baseline and for analytical errors.

The electrolyte levels used for this endpoint are all the measurements analyzed in the central lab (ion-specific electrode or ISE). Serum albumine levels, if available on the same blood sample and point-of-care chloride assessments from the blood gas analyzer, performed within 2 hours of the ISE analysis, are recorded to cross-check and to assess potential interference in a sensitivity analysis.

→ Rationale: the NaCl-rich arm could be associated with a higher occurrence of hyperchloremia.(4, 21)

- **Fluid retention and diuretic use**

  - Time between randomization and the first administration of an intravenous loop diuretic (exact timestamp of the first administration is collected)
  - Proportion of ICU days during which IV loop diuretics were administered (collected without their specific timestamp)
  - Cumulative fluid balance from ICU admission to the morning of the first ICU day on which an IV loop diuretic is prescribed

→ Rationale: the NaCl-rich arm could be associated with a higher occurrence of clinically relevant fluid retention.(4)

- **Occurrence of hyperglycemia and hypoglycemia**

  - Proportion of glycemia > 180 mg/dL over total number of glucose assessments.
  - Mean daily glycemia of every ICU day
  - Occurrence of hypoglycemia < 70 g/dL analyzed as the number of patients with at least one event

  Each day of ICU admission, all glucose assessments on the blood gas analyser are collected, without their specific timestamp.

  → Rationale: the NaCl-poor arm always contains glucose and could therefore be associated with a higher occurrence of hyperglycemia.

- **Acute kidney injury**

  - Occurrence of new-onset stage acute kidney injury (KDIGO stage 2 or 3) from the third ICU day after randomization (number of patients with at least one event) (33)

  This metric is calculated as follows: to determine AKI, serum creatinine levels for a given ICU day are based on morning routine sampling, regardless of the exact timing. This means that a creatinine measurement taken at 6 AM on ICU day 2 can still be used to assess AKI on ICU day 3. For urine output criteria, the total urine output over the previous 12 and 24 hours is evaluated at 8 AM each ICU day, when the daily fluid balance is assessed. Note: KDIGO Stage 1 is not assessed in this study. Only KDIGO Stage 2 and Stage 3 criteria are considered for AKI classification.

STAGE	SERUM CREATININE CRITERIA	URINE OUTPUT CRITERIA
KDIGO stage 1	Serum creatinine increases with a factor 1.5 to 1.9 times from baseline* *or* Serum creatinine level increases with at least 0.3 mg/dL in 48 hours	< 0.5 mL/kg/hr for 6–12 hours
KDIGO stage 2	Serum creatinine increases with a factor 2 to 2.9 from baseline*	< 0.5 mL/kg/hr for ≥ 12 hours
KDIGO stage 3	Serum creatinine increases with at least a factor 3 from baseline* *or* Serum creatinine level reaches at least 4 mg/dL *or* Initiation of renal replacement therapy	< 0.3 mL/kg/hr for ≥ 24 hours OR anuria for ≥ 12 hours

Table 2: overview of KDIGO criteria. * Baseline creatinine is the lowest creatinine level in the preceding 3 months, if unavailable in the preceding 6 months, if unavailable the lowest value assessed within the first 48 hours of admission.

→ Rationale: the NaCl-rich arm contains more chloride (which has been proven to be associated with hyperchloremia and AKI) and could lead to more fluid accumulation.(14) To determine AKI, creatinine levels on a specific ICU day are the ones taken during morning routine sampling, no matter the exact timing. This means that creatinine sampled at 6AM on the second ICU day can still be used to diagnose AKI on the third ICU day. To determine the urine output criteria, at 8AM it is checked how much urine was produced over the past 12 and 24 hours. This method used to determine AKI thus primarily reflects AKI that occurred the previous day. We only consider AKI determined on the third ICU day after randomization to better distinguish AKI caused by the intervention from AKI resulting solely from the underlying disease.

- New-onset need for RRT from the second ICU day after the ICU Day of randomization
- Days without renal replacement therapy at D90

This metric is calculated by assigning one point for each day during the 90-day measurement period that the patient is both alive and free from renal replacement therapy (RRT)

Renal replacement therapy is defined as the use of continuous renal replacement therapy, peritoneal dialysis or intermittent hemodialysis. The presence of continuous renal replacement therapy is counted when this type of support has been in place during an ICU Day. Periods with up to 3 days between intermittent hemodialysis are counted as days with RRT, e.g. if a patient received IHD on day 1, did not receive IHD on days 2–4, and received IHD again on day 5, the patient is considered to have been on RRT for the entire period from day 1 through day 5.

→ Rationale: the NaCl-rich arm contains more chloride (which has been proven to be associated with hyperchloremia and AKI) and could lead to more fluid accumulation.(14) We only consider RRT from the second ICU day after randomization to better distinguish AKI caused by the intervention from AKI resulting solely from the underlying disease.

- **Mechanical ventilation**

  - New-onset need for mechanical ventilation from the second ICU day after the ICU Day of randomization
  - Ventilator-free days at D90

  This metric is calculated as one point for each day during the measurement period that patients are both alive and free of mechanical ventilation. Mechanical ventilation is defined as invasive or non-invasive ventilation (CPAP or with any amount of pressure or volume support but excluding high-flow nasal oxygen). On each ICU Day (Figure 1), the presence of mechanical ventilation is counted when this type of support has been in place. The days following extubation are only counted as ventilator-free days when no re-intubation happens within 48 hours of extubation.

  → Rationale: the NaCl-rich arm contains could lead to more fluid accumulation, which has been proven to be associated with a prolonged ventilatory support.(11)

- **Mortality and length of stay**

  - Days alive and out of hospital at 90 days after ICU admission (DAOH90). If a patient was discharged and later readmitted, both admissions count towards the total hospitalization days. Mortality is penalized and receives a value of DAOH of zero. DAOH is determined at day 90 after ICU admission.
  - ICU and hospital mortality at ICU discharge or at 90 days after ICU admission whichever comes first.
  - ICU and hospital length of stay

  ICU length of stay includes referral to other ICU's during the same admission.
  Hospital length of stay includes transfers to other hospitals but excludes discharges to rehabilitation wards within a hospital.

1.4.5.2 Efficacy endpoints

- **Daily and cumulative sodium, chloride and glucose administration:** daily and cumulative sodium, chloride and glucose administration from all sources except for non-study fluid creep and oral intake. For blood products, estimated values of sodium and chloride content are used.
- **Fluid balance:** Daily and cumulative fluid balance on ICU days, excluding (calculations of) insensible losses. From the moment RRT or IV loop diuretics are started, fluid balance data are analyzed separately from the patients without those interventions. Fluid balance assessments are discontinued from the ICU Day when the urinary catheter is removed, or bladder irrigation is initiated.

The necessary assessments for these endpoints are summarized in Table 3.

		Daily volume (mL)	Daily sodium (mmol)	Daily chloride (mmol)	Daily glucose (g)
Volume IN	Study-arm maintenance	x	x	x	x
	Study-arm fluid creep	x	x	x	x
	Non-study fluid creep	x			
	Non-study maintenance and replacement fluids	x	x	x	x
	Non-study resuscitation fluids (>500 mL/h)	x	x	x	x
	Nutrition (enteral and parenteral)	x	x	x	x
	Blood products	x	x	x	x
	Oral Intake	x			
Volume OUT	Urine	x	(SALADIN nested substudy)	(SALADIN nested substudy)	
	Net ultrafiltration (RRT)	x			
	Gastric fluid (excl. irrigation volumes)	x			
	Drain outputs	x			
	Diarrhea if precisely collected	x			

Table 3: Different components collected in the detailed assessment of fluid balance. Fluids are collected per ICU Day (Figure 1). The first ICU Day spans from admission to 8AM the following calendar day; subsequent ICU days run from 8 AM to 8 AM the following calendar day; the day of ICU discharge runs from 8AM to the moment of discharge.

→ Rationale: to demonstrate the difference in sodium and chloride burdens due to the intervention, and ensuing impact on fluid balance. As a reference: a healthy human diet contains 100 mmol or 2.3g of sodium, 1L of NaCl 0.9% contains 154 mmol or 3.5g of sodium.(2, 34)

1.4.6 Exploratory endpoints

- **Serum urea-to-creatinine ratio**

  Difference in the serum urea-to-creatinine ratio measured every other ICU day from the first morning after randomization in patients not receiving renal replacement therapy.

  Serum creatinine levels are routinely assessed, urea is not always standard-of-care, but will not lead to additional sampling as this will be performed together with routine morning blood sample.

  Patients under renal replacement therapy are excluded from this exploratory endpoint, and urea assessments are discontinued from the moment RRT is started.

  → Rationale: the NaCl-rich arm contains more sodium, which has been proven in animal and human studies to be associated with increased muscle catabolism. Serum urea-to-creatinine ratio is an established marker of muscle catabolism in critically ill patients.(35-37)

1.4.6.1 Exploratory endpoints in the SALADIN nested substudy

- **Sodium and chloride balance**

  The daily and cumulative sodium and chloride balance (study and non-study intake minus urinary output) is calculated until the ICU day on which bladder catheter removal, initiation of bladder irrigation, start of renal replacement therapy, or ICU discharge occurs, whichever comes first

  → Rationale: to demonstrate the difference in sodium and chloride balance due to the intervention, the time it takes to realign intake versus output and the time to excrete the sodium and chloride that is administered during the treatment of critical illness. As a reference: a healthy human diet contains 2.3g of sodium, 1L of NaCl 0.9% contains 3.5g of sodium.(24)

- **Measured daily body weight**

→ Rationale: to correlate with fluid balance (to correct for insensible losses).

- **Calculations of solute-free and electrolyte-free water clearance**

  Solute-free water clearance (FWC) is calculated using urine volume per day, urine osmolality (assessed on study-specific urine collections) and plasma osmolality (assessed within standard of care); electrolyte-free water clearance (EFWC) is calculated using urine volume per day, urine sodium and potassium (both assessed on study-specific urine collections) and serum sodium (assessed within standard of care).

  → Solute-free water clearance CH_2O and electrolyte-free water clearance (EFWC) CeH_2O are used to assess fluid balance, renal water handling, and the effects of IV fluids on body water and electrolyte homeostasis. These parameters help evaluate how the kidneys regulate water excretion vs. retention, which is crucial in conditions like fluid overload, dehydration, and electrolyte imbalances.

- **Volume kinetics assessments**

  Total volume and sodium intake, body weight and urine volume, sodium, chloride and potassium output will be correlated with measures of plasma dilution based on the standard-of-care measurements of hemoglobin, albumin and sodium, which are collected together with the timing of their assessment.

  → Rationale: volume kinetics is a pharmacokinetic-based mathematical approach used to describe the distribution, elimination, and effects of intravenous (IV) fluids in the human body. Developed primarily by Hahn et al., this model is particularly useful in critical care and anesthesia to understand how different fluid types behave in circulation. Volume kinetics models the movement of IV fluids between the central compartment (plasma volume), the intracellular compartment and urinary elimination. We aim to assess how the extracellular and intracellular compartments are maintained under the different study arms. Current guidelines on maintenance fluids recommend daily needs based on old dietary guidelines and have been challenged recently.(38)

- **Bioelectrical Impedance Analysis**

  Bio-Electrical Impedance Analysis (BIA) measurements will be performed using a touch i8 multi-frequency analyzer (Maltron International, Essex, UK) as per the manufacturer's instructions. Two electrodes will be placed on the hand and two on the forefoot at each side (in total 8 electrodes, 4 on the left and 4 on the right), and bioelectrical impedance will be measured at four frequencies (5, 50, 100, and 200 kHz), with STAR methodology allowing segmental analylis with the patient in a completely supine position. The multi-frequency approach allows differentiation between intracellular and extracellular as well as intravascular and extravascular compartments, providing critical insights into fluid status without exposure to radiation or other risks

  Measurements will be conducted at least once every three ICU days starting from the day of randomization.

  Parameters assessed:
  - Total Body Water (TBW), Intracellular Water (ICW), and Extracellular Water (ECW) in liters and percentages, and ECW/ICW ratio
  - Intravascular (IVF) and extravascular (EVF) fluid, and EVF/IVF ratio
  - Volume excess (VE)
  - Fat-Free Mass (FFM, kg and %), Fat-Free Mass Hydration (FFMH, %), and Fat Mass (FM, kg and %)
  - Protein mass (kg), Mineral mass (kg), Bone mass (kg), Muscle mass (kg)
  - Resting Metabolic Rate (RMR), Glycogen deposits (g)
  - Phase angle and Malnutrition Index

  → Rationale: BIA measurements offer valuable data on fluid distribution, hydration status, and nutritional assessment. BIA-derived parameters, particularly the ECW/ICW and EVF/IVF ratio and volume excess, are crucial for evaluating fluid accumulation and its prognostic impact in critically ill patients. The correlation of BIA data with fluid and electrolyte balance, measures of free water

clearance, body weight, volume kinetics calculations and clinical outcomes in the SALADIN nested substudy will contribute to a deeper understanding of the intervention's effect on fluid management and patient outcomes in the ICU setting.(29)

1.5 STUDY DESIGN

Investigator-initiated, multi-center, prospective, randomized, stratified, double-blind phase IV parallel grouped trial. Primary and all safety and efficacy outcomes will be analyzed according to the intention-to-treat principle for all randomized patients who provided informed consent.

1.6 STUDY SETTING

The CRUSADERS-trials is a multi-center study in four different Belgian mixed ICU's of different sizes in a broad range of critically ill adult patients. To avoid performance bias, all study fluids are blinded.

1.7 PARTICIPANT ELIGIBILITY CRITERIA

1.7.1 Inclusion criteria

1. At least 18 years of age
2. Patients who are admitted to the ICU for medical or surgical emergencies, including complications of elective surgery
3. The treating physician expects the patient will still require ICU care in two days, indicating a severe or complex condition at enrollment
4. The patient is expected to receive at least 300 mL of fluid creep or at least 1L of maintenance fluid according to study arm during the first 24h after inclusion

1.7.2 Exclusion criteria

1. A contraindication to hypotonic fluids due to risk of brain edema (including traumatic brain injury, major stroke, intracranial/subarachnoid hemorrhage, meningoencephalitis, intracranial malignancies…), with the timing and clinical judgment left at the discretion of the treating physician.
2. Hyponatremia below 131 mmol/L at admission
3. Admission solely for treatment of fluid accumulation due to cardiac decompensation, without other acute medical conditions requiring ICU-level care. Note: Patients with heart failure as a comorbidity, those on chronic diuretic therapy, or presenting with edema/bilateral lung infiltrates due to other conditions (e.g., sepsis, pneumonia) are not excluded.
4. Patient's death is deemed imminent and inevitable, admission for palliative care or admission solely for organ donation
5. Patient receiving chronic renal replacement therapy
6. Patients referred after a stay of more than 24 hours in another ICU
7. Patients randomized in CRUSADERS before
8. Patient is co-enrolled in an unapproved concomitant ICU-trial or in any trial with an intervention that affects fluid administration or fluid balance

We will not exclude patients enrolled in other interventional trials unless the protocols of the two trials collide (e.g. an intervention that consists of different fluid strategies (either in volume or type) or their interventions have an impact on fluid balance (e.g. diuretic use)). A continuously updated list of ICU-trials approved for co-enrollment, as agreed upon by the TSC, will be maintained.

We will not exclude pregnant patients and do not mandate pregnancy testing women of childbearing potential (WOCBP) in this low-risk, low-intervention context. See also: Section 1.14 Ethical and Regulatory Considerations.

1.7.3 Additional exclusion criteria for the SALADIN nested substudy

1. Patients expected to require renal replacement therapy within 24 hours
2. Increased insensible fluid losses: burns, extensive wounds or skin defects or massive diarrhea,…
3. Patients without a urine catheter
4. Patients expected to require bladder irrigation within 24 hours
5. Patients on chronic treatment with loop or thiazide diuretics (including combination preparations)

1.8 STUDY PROCEDURES

For an overview of the study visits, we refer to the timeline of the study procedures in the Study Schedule of Assessments Flowchart (Table 1).

1.8.1 Recruitment

All patients admitted to an active trial site will be considered for participation. Patients will be eligible if they comply with the inclusion and exclusion criteria above. We aim to include patients as early as possible once they meet the inclusion criteria, while allowing a flexible time frame to accommodate ICU workload and assess the need for prolonged intensive care.

1.8.1.1 Patient identification

All patients admitted to the ICU of a study site will be screened for eligibility upon admission or shortly thereafter, ensuring randomization before the patient's ICU stay reaches the second 12:00 noon. Training will be structured to ensure that a physician trained in the study procedures is available on-site 24/7.

1.8.1.2 Screening

Screening will be performed based on the eligibility criteria of the trial. The following data will be reviewed prior to inclusion to verify eligibility for each potential trial participant:

- Age ≥ 18 years of age
- Type of admission to exclude uncomplicated elective surgery
- Reason for admission to exclude neurological emergencies, including traumatic brain injury, treatment of fluid overload, futile or palliative care
- Source of admission to exclude referred patients after a stay of more than 24 hours in another ICU
- Chronic renal replacement therapy
- Hyponatremia < 131 mmol/L. To prevent screening delays, a point-of-care sodium measurement using a blood gas analyzer at admission can be used. If unavailable, a sodium value of at least 133 mmol/L from a test performed within the past 24 hours may be used instead.
- Previous enrollment in CRUSADERS or participation in unapproved concurrent trials

1.8.2 Consent

- The Principal Investigator (PI) at each participating site holds ultimate responsibility for obtaining informed consent from participants at their site. The PI ensures that any individual delegated to participate in the informed consent process is appropriately authorized, adequately trained, and competent to do so, in accordance with the ethically approved protocol, the principles of Good Clinical Practice (GCP), and the Declaration of Helsinki. Delegation of the consent process is permitted, and the details of such delegation must be documented in the delegation log.
- To maximize the duration of exposure to the intervention and better distinguish its effect, a **trapped deferred consent procedure** is implemented (Figure 4). This approach aligns with the study's low-interventional design. Additional justifications for this method stem from the specific ICU setting, as outlined below:
    - patients admitted to the ICU are often unable to provide written consent immediately upon admission, due to the severity of their condition, altered mental status or reduced concentration, or the administration of sedative medications… Studies on decision-making under stress demonstrate that individuals in high-pressure scenarios exhibit reduced comprehension, delayed processing, and impaired recall of information.(39, 40)
    - close family members or legal representatives may not always be available at the time of admission or during the initial days of hospitalization, or – due to the overwhelming character of an ICU admission – may require time to deliberate or consult with other relatives before providing consent.

- the CRUSADERS trial Patient and Public Involvement (PPI) provided insights on informed consent in critical care and highlighted significant challenges in obtaining informed consent particularly in acute situations. The key concerns identified include:
  - critical illness and emergency situations induce high emotional distress, impairing a patient's or their surrogate's cognitive capacity to process complex medical information.
  - multi-page consent forms, even when written in lay terms, can be overwhelming for both patients and surrogates.
  - the urgency of interventions in ICU settings often leaves little time for thorough discussion and comprehension of consent materials. PPI discussions emphasized that family members, when acting as surrogates, might feel rushed or pressured, further impairing their ability to make informed and autonomous decisions.
  - the hospital environment, unfamiliar terminology, and severity of the situation contribute to emotional distress and decision fatigue.

Therefore, the Trial Steering Committee advised that written informed consent should be sought **at the earliest opportunity**.

- Content of the Informed Consent discussion: within this trapped procedure, the Principal Investigator (PI), a qualified Sub-Investigator or a delegated party, who has completed study-specific training, conducts a comprehensive discussion with the potential participant or their legally authorized representative. During this discussion, participants are informed that their participation is entirely voluntary and that they have the right to withdraw consent at any time without penalty. They are also informed that their records may be accessed by authorized personnel and competent authorities for study-related purposes, while confidentiality will be maintained to the extent permitted by applicable laws and regulations.

  The conversation includes a clear explanation of the study's nature and objectives, the potential risks associated with each intervention arm, and the implications of receiving standard-of-care treatment outside the study in the event of non-participation. This process ensures that participants or their representatives are fully informed, enabling them to make an educated and voluntary decision about study participation. Additionally, potential participants are given the opportunity to ask questions to address any concerns or seek further clarification.

1.8.2.1 Patient is capable of giving written informed consent at the time of admission

- The patient is considered capable of giving written consent if all below conditions are fullfilled:
  - understands the research purpose and nature.
  - is aware of study details, including benefits (or lack thereof), risks, and burdens.
  - knows alternatives to participation, including standard-of-care where the treating physician determines maintenance fluid therapy, and fluid creep is addressed per standard pharmacy procedures.
  - retains relevant information long enough to make an effective decision.
  - makes a free and autonomous choice without coercion.
  - is capable of making this specific decision at the required time, even if their decision-making capacity fluctuates.
- Process for obtaining written informed consent:
  - A written, dated and signed informed consent is obtained from the subject before randomization.The ICF is provided in a language sufficiently understood by the participant. In case the subject is unable to read, an impartial witness must attest the informed consent.
  - The patient receives an information leaflet and a copy of the informed consent document. These documents are approved by the Belgian authority and an Ethics Comittee and comply with Good Clinical Practice (GCP), local regulatory, and legal requirements.
  - The following information is added to the electronic patient file: date informed consent was obtained, name of the investigator who obtained ICF.

1.8.2.2 Patient is not capable of giving written informed consent at admission

In the CRUSADERS trial, informed consent is first obtained from a medical doctor who is part of the treating team but is independent of the trial, unless a legal representative is available at admission and the situation allows for a complete discussion (see 1.8.2). Consent by the medical doctor can be given in person or, if necessary, after telephone consultation to ensure timely inclusion of eligible patients. When consent is obtained via telephone, a signed written confirmation must be provided on the next working day to formally document approval.

Written informed consent is obtained from the legal representative at the earliest opportunity, which may not necessarily be the first time the representative is encountered by the treating team or a trial investigator. The timing of this consent procedure takes into account the priority of addressing the patient's critical condition, including discussions about diagnosis, therapy, and prognosis. The explanation of the trial is carefully introduced to ensure it does not detract from the immediate and primary focus on the patient's medical care.

The legal representative of a patient is:

➢ For adults for whom a guardian has been appointed by court decision: the guardian.
➢ For temporarily or permanently incapacitated individuals without a guardian: the representative designated by the patient through a written power of attorney.
➢ For incapacitated individuals without a guardian or designated representative: in descending order of priority, (1) the spouse or legal/actual cohabiting partner, (2) an adult child, (3) a parent, or (4) an adult sibling.

At the discretion of the treating physician, other blood relatives may act as the legal representative, but only if they are deemed trustworthy and able to act in the best interest of the patient

If information about the participant's legal representative is unavailable, the investigator will attempt to obtain the info through alternative sources, such as the participant's general practitioner, police, or nursing homes. In such cases, it may take some time to determine that no legal representative can be identified. If no legal representative is identified within a reasonable time frame and the participant remains incompetent, written consent is obtained from a second medical doctor of the treating team who is independent of the trial and the trial intervention will be continued until the patient regains capacity. All efforts to identify the participant's legal representative will be thoroughly documented in the electronic patient file.

- As soon as the patient regains full capacity (for definition: see above), written informed consent is obtained directly from them. If they do not consent for further treatment or follow up, it is separately discussed whether the data collected up to this point can be used, or whether they wish to have all data deleted. In the latter case, a new patient will be recruited to reach the necessary sample size.

- If the patient dies before informed consent from a legal representative has been obtained, and the patient has been correctly included in the trial, the collected data will be kept for analysis.

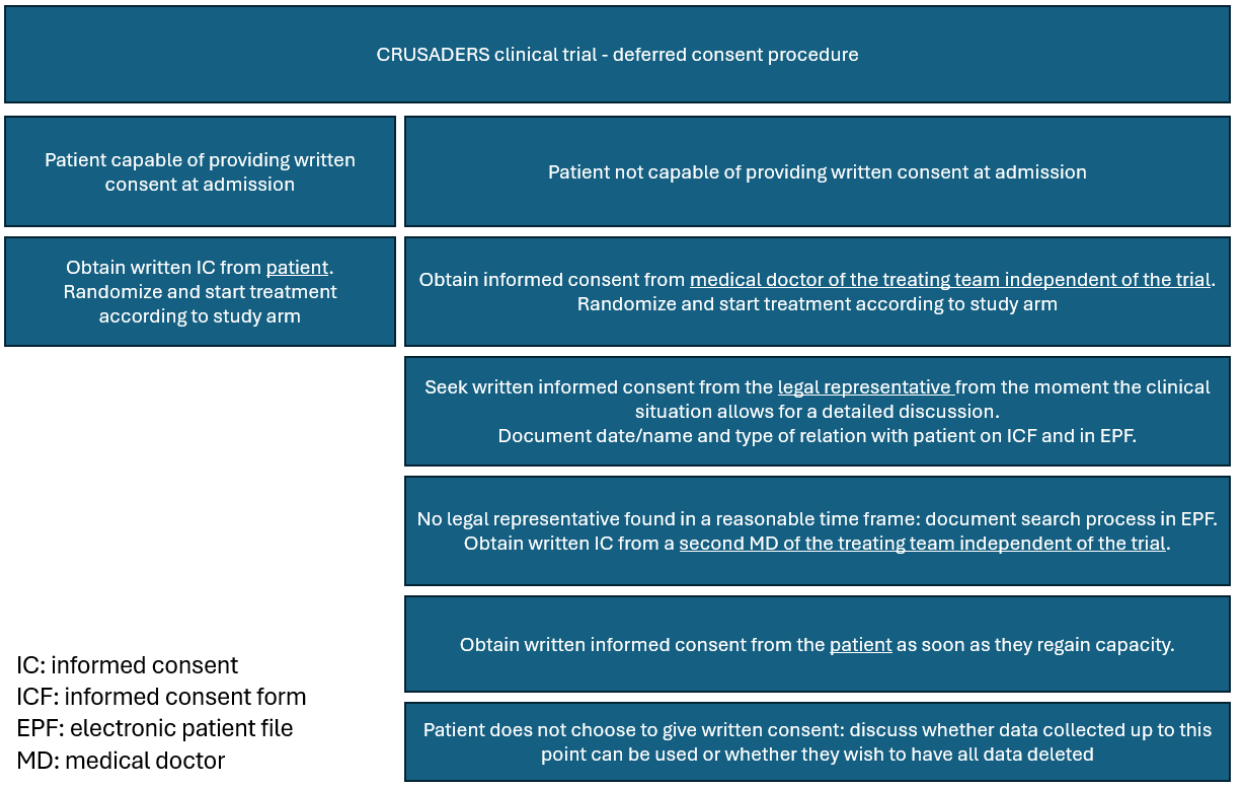


Figure 4: Summary of the CRUSADERS trapped deferred informed consent procedure

1.8.3 Study Randomization

Eligible patients are randomized before the patient's ICU stay reaches the second 12:00 noon (see Figure 1). Patients who participate in the SALADIN nested substudy need to be randomized before the first urine is dismissed (usually at the end of the first ICU Day).

All physicians caring for patients in participating ICUs and who will have undergone study-specific training will be eligible to enroll patients in the trial and will be eligible to care for and perform the interventions in the trial participants. All participating ICUs will receive written and oral instructions about the trial procedures.

Patients are randomised 1:1 using stratified randomization where trial site, mechanical ventilation at randomization and surgical admission are used as stratifiers. Per stratum, permuted block randomization will be used with a variable block size. Full details will be provided in a separate document with restricted access. The allocation sequence list and block sizes are only known by the statistician and data manager, and remain concealed from the investigators until the last patient has completed follow-up.

Patients in the trial are randomized to one of the two study arms, each corresponding to a specific fluid strategy. To maintain operational efficiency and minimize logistical challenges, each study arm is assigned a letter (e.g., A and B) for a one-month period. During this month, patients are randomized to either letter A or B.

After the one-month period, study treatment for patients already randomized to A or B continues unchanged for another 28 days to complete their protocol. However, new patients enrolling in the trial are randomized to two new letters (e.g., C and D), which correspond to the same two treatment arms.

The process continues with two new letters assigned each month to represent a study arm. However, these letters can be reused after a sufficient period has passed, such as when the same letter has not been used in the ICU for at least two months.

This sequential letter assignment process ensures that the study maintains a balance between reducing the risk of unblinding (by regularly changing the labeling of study arms) and avoiding excessive storage demands (by limiting the quantity of fluids required for each lettered arm in the ICU).

The allocation and transition process is structured as follows and clarified in Figure 5 below.

The pharmacy manages these transitions to ensure uninterrupted supply and proper logistics during the overlap periods.

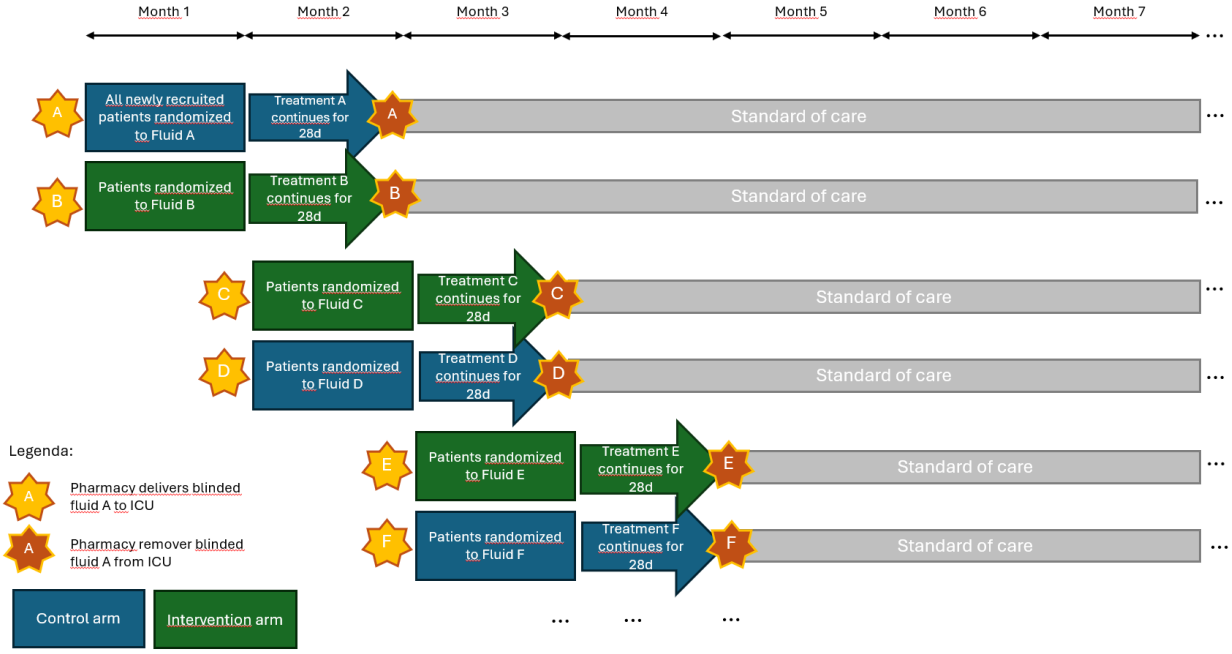


Figure 5: Overview of the randomization process and the concomitant study fluid treatment available in the department at any given time.

1.8.4 Blinding

The study fluids consist of commonly used, market-authorized fluids that are produced as usual according to GMP (Good Manufacturing Practice) standards. The fluids are placed in opaque, sealed bags that mask their contents and are identical in appearance.

Study participants, care providers and investigators are blinded to the study treatment. Only pharmacists are unblinded as they receive the study fluids and deliver the blinded fluids to the intensive care ward. No unblinded study fluids are present in the ICU department at any time during the trial.

The timing of final unblinding of all study participants is after the creation of the locked analysis data set, which takes place after the last patient visit.

1.8.5 Unblinding

All fluids used in this study are administered within their market authorizations, and any potential side effects, such as electrolyte disturbances or hyperglycemia, are routinely monitored and treated during the ICU stay. It is important to acknowledge that most of these potential side effects are commonly observed in conditions unrelated to the study treatments. Consequently, it is **highly unlikely that unblinding will be required at any point during the trial.**

In the rare event a code is required to be unblinded, a formal request for unblinding will be made by the Investigator/treating health care professional. The investigator cannot be required to discuss unblinding if he or she feels that emergent unblinding is necessary.

- If the person requiring the unblinding is a member of the Investigating team then a request to the PI, or their delegate will be made and the unblinded information obtained.

- If the person requiring the unblinding is not the CI/PI then that health care professional will notify the Investigating team that an unblinding is required for a study subject and an assessment to unblind should be made in consultation with the clinical and research teams.

The coding system in blinded studies should include a mechanism that permits rapid unblinding (ICH GCP 5.13.4). In the case of the CRUSADERS study, the quickest method is to open the sealed plastic

bag, a procedure that should only be performed in true emergencies. Upon knowledge of the treatment allocation details the CI/PI or treating health care professional will continue to deal with the participant's medical emergency as appropriate.

The CI/PI documents the breaking of the code and the reasons for doing so on the (e)CRF/data collection tool, in the site file and medical notes. It will also be documented at the end of the study in any final study report and/or statistical report.
The CI/Investigating team will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break.
The CI/PI will also notify the relevant authorities. The written information will be disseminated to the Data Safety Monitoring Committee for review in accordance with the DSMB Charter.

1.8.6 Baseline data

1.8.6.1 Demographic, medical history and admission type data

- Age
- Sex at birth
- Ethnicity (assessed because daily sodium intake is culturally influenced, which may affect the impact of the intervention): low-to-moderata salt intake ethnicities: North European, Southern European, Middle Eastern, Other/Non-Categorized versus higher salt intake ethnicities: North African, Asian, Afro-descendant, Central European.(41) Since this parameter is collected to determine extrinsic (cultural) rather than intrinsic ethnic factors, it is self-reported by the participant or their family.
- Medical history: chronic comorbidities: HEFrEF (left ventricular ejection fraction $\leq$ 40%), chronic kidney disease (eGFR < 60 mL/min/1.73m²), chronic liver disease Child-Pugh B or C, diabetes mellitus type 1 and 2, hematologic or metastatic cancer
- Clinical Frailty Scale, obtained from patient, legal representative, family, general practitioner, patient history or medical records.
- Body weight – body height, measured or estimated or asked directly to the patient if feasible, in kg and cm respectively at admission, to calculate BMI,
- Date and time of admission to the hospital
- Date and time of admission to the ICU
- Source of admission to the ICU: emergency room (ER) or prehospital setting, operating room (OR), hospital ward, cardiac intervention lab, another ICU, other
- Type of admission: medical (defined as no surgery within 24h of admission), emergency surgery or complicated elective surgery
- Main reason for admission: infection/sepsis, neurological (excl infection), cardiac (excl infection), respiratory (excl. infection), renal and electrolyte disorders, endocrine and metabolic disorders (excl infection), gastrointestinal tract (excl infection), liver (excl infection), trauma, intoxication, other
- Sepsis or septic shock at admission, according to Sepsis 3.0 Guidelines.(42)
- Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)(43). Additional variables besides Age and Acute surgical reason for admission:
    - Lowest blood pressure within 24h of ICU admission ('0' if cardiac arrest in first 24h)
    - Hematological malignancy or metastatic cancer
    - Use of continuous infusion of vasopressor/inotropes within 24h of ICU admission
    - Use of respiratory support (invasive, non-invasive or continuous CPAP) within 24h of ICU admission
    - Use of renal replacement therapy (acute or chronic, intermittent or continuous) within 24h of ICU admission
- Additional baseline data for SALADIN nested substudy:

- Loop or thiazide diuretics as chronic medication, including combination preparations.
- Total amount of NaCl 0.9%, PlasmaLyte, Ringer's solution, iso-oncotic albumin, starches or gelatins in the emergency room, operating room and/or hospital ward in the 24 hours before ICU admission.

1.8.6.2 Clinical and lab variables at admission to determine SOFA score (within standard of care)

- Clinical organ dysfunction criteria at admission to determine SOFA-score:
  - Lowest mean arterial blood pressure (MAP) within 24h of ICU admission
  - Administration of vasopressors throughout the ICU Day (see Figure 1), collected as the following yes/no variables of
    - a dose below or equal to 0.1 µg/kg/min (nor)epinephrine
    - a dose higher than 0.1 µg/kg/min (nor)epinephrine
    - any dose of dobutamine
    - a dose below or equal to 5 µg/kg/min dopamine
    - a dose between 5 and 15 µg/kg/min of dopamine
    - a dose higher than 15 µg/kg/min dopamine
  - Urine output during first ICU Day
  - Pre-sedation Glasgow Coma Scale
- Additional lab variables to determine SOFA-score:
  - paO2 / FiO2 ratio on a blood gas analysis within 1 hour of admission,
  - platelet count
  - serum bilirubin

1.8.6.3 Baseline lab variables (within standard of care)

- Serum Na, Cl and albumine routinely assessed in the central lab by ion-selective electrode (indirect potentiometry) within a window of 6 hours before or after admission.
- Point-of-care sodium and chloride as routinely assessed on the blood gas analyzer, performed within 2 hours of the above ISE analysis
- Serum creatinine assessed in the central lab within a window of 6 hours before or after admission.

1.8.7 Study assessments

1.8.7.1 Treatment phase

The treatment phase, during which the intervention takes place, begins as soon as possible after randomization. Maintenance fluids and line patency fluids must be initiated or replace current maintenance within two hours, while medications are first dissolved in the study treatment at the next scheduled administration requiring dissolution.

The treatment continues until the patient is discharged from the ICU or until the study-specific fluid is no longer available in the department (according to the Randomization Schedule: at least 28 days after randomization).

If the patient is readmitted to the ICU while the study fluid corresponding to their randomized letter (as per the Randomization Schedule) is still available in the department, the study treatment should resume according to the assigned study arm.

1.8.7.1.1 Laboratory variables, to be collected daily (morning values if more than one) (within standard of care, with the exception of urea):

- Morning routine serum Na, Cl and albumine, assessed in the central lab by ion-selective electrode (indirect potentiometry), including their time of sampling. ICU days start at 8 AM, but routine blood samples are often collected earlier. Regardless of timing, morning samples count toward the ICU day beginning at 8 AM.
- Point-of-care sodium and chloride routinely assessed on the blood gas analyzer, performed within 2 hours of the above ISE analysis.
- Serum creatinine, morning value, to determine AKI stage and urea-to-creatinine ratio. ICU days start at 8 AM, but routine blood samples are often collected earlier. Regardless of timing, morning samples count toward the ICU day beginning at 8 AM.
- Serum urea is measured together with the first morning routine blood sampling after randomization and then every other day, except when RRT has been started.
- Every routine blood glucose assessment throughout the day (measured on the POCT blood gas analyzer)

1.8.7.1.2 Organ support, AKI, diuretic treatment and presence of contraindications:

- Use of non-invasive mechanical ventilation, including CPAP, but excluding HFNC throughout the ICU Day (see Figure 1)
- Use of renal replacement therapy throughout the ICU Day (see Figure 1)
- Baseline creatinine, defined as the lowest creatinine level in the preceding 3 months, if unavailable in the preceding 6 months, if unavailable the lowest value assessed within the first 48 hours of admission.
- Total urine output over the previous 12 and 24 hours, evaluated each ICU day at the time the fluid balance is assessed
- Exact time of first new-onset intravenous loop diuretic administration
- Concomitant medication: Administration of intravenous loop diuretics (furosemide (Lasix®, bumetadine (Burinex®)), throughout the ICU Day (see Figure 1), collected as a cumulative dose of each of both medications.
- Administration of vasopressors throughout the ICU Day (see Figure 1), collected as a yes/no variable when norepinephrine, epinephrine or dopamine are used.
- Presence of a new-onset neurological contra-indication to study maintenance fluids (risk of brain edema, e.g. traumatic brain injury, subarachnoidal hemorrhage, hemorrhagic or ischemic stroke, meningitis or encephalitis,…). Note that the other potiential contraindications to study maintenance fluids (hyponatremia, hypernatremia and hyperglycemia) will be collected as study assessments.

1.8.7.1.3 Standard-of-care fluid balance assessments

Fluid balance parameters are collected daily for each ICU day, from ICU admission until ICU discharge or until the study fluid is discontinued and removed from the department, whichever comes first. The definitions of ICU days are illustrated in Figure 1. Fluid balance data are recorded at a fixed time each morning.

In cases of bladder irrigation or after bladder catheter removal, fluid balance calculation is discontinued, but fluid INPUT and other fluid OUTPUT remain to be collected.

- Fluid INPUT
  - Study maintenance fluids, volume in mL
  - Study creep fluids, volume in mL
  - Non-study maintenance fluids and replacement fluids, volume and type (Table 4)
  - Non-study resuscitation fluids (defined as crystalloids > 500 mL/h or any artificial colloid), volume and type (Table 4)

- Enteral nutrition, volume and type (Table 4)
- Parenteral nutrition, volume and type (Table 4)
- Recorded oral intake, volume in mL
- Cumulative volume of blood products (plasma, packed red blood cells, platelets), volume and type (Table 4)
- Remaining volume IN must be Non-study fluid creep, volume in mL, volumes to be cross-checked with fluid balance in electronic charts

Crystalloids	**Colloids and blood products**
NaCl 0.9% (note that higher concentrations, including mannitol 15-20% are considered fluid creep)	Albumine 4-5% / SOPP® (note that higher concentrations are considered fluid creep)
PlasmaLyte	Albumine 20% (considered fluid creep, but to be collected separately)
Ringers/Hartmann's solution	Gelofusine
NaCl 0.9% in glucose 5%	Geloplasma/Gelaspan
Sodium bicarbonate 1.4% (note that higher concentrations are considered fluid creep)	Packed red cells
NaCl 0.45% in glucose 5%	Fresh frozen plasma
Glucion 5 or 10%	Platelet transfusion
GNaK	**Enteral and parenteral nutrition**
Glucose 5%	All locally available enteral formulations
Glucose 10%	All locally available parenteral formulations
Glucose 20%	
Glucose 50%	

Table 4: Fluid types to be collected (depending on local formularium not all fluid types will be used)

- Fluid OUTPUT
  - Urine production (netto, so this parameter cannot be accurately measured in cases where bladder irrigation is performed.)
  - Net ultrafiltration by renal replacement therapy
  - Gastric fluid (netto, so do not consider readministered residual gastric volumes)
  - Cumulative drain outputs (e.g. ascites, pleural fluid, surgical drains,…) (netto, so do not consider irrigations)
  - Diarrhea, only if precisely collected (e.g. Flexiseal, Dignishield) (netto, so do not consider irrigations)

1.8.7.1.4 Specific serious adverse reactions (see below)

The SAEs listed below are recorded by the study team in a dedicated part of the eCRF (RedCAP) (See section 1.10 Safety Recording and Reporting) and retrieved there by the data personnel.

- New-onset (> 48h after randomization) severe hyponatremia (<125 mmol/L) with seizures or profound lethargy unexplained by sedation or other disease
- New-onset (> 48h after randomization) severe hypernatremia (>155 mmol/L) with seizures or profound lethargy unexplained by sedation or other disease
- New-onset central pontine myelinolysis (symptoms starting > 48h after randomization), confirmed on MRI
- New-onset (> 24h after randomization) clinical refeeding syndrome defined as severe hypophospatemia < 1 mg/dL or < 0.32 mmol/L + hypokalemia < 3 mmol/L + clinical picture with symptoms such as fluid retention, edema, extreme muscle weakness, cardiac arrythmias, heart failure, respiratory failure, seizures or a combination of the above.

- New onset (> 24h after randomization) Wernicke encephalopathy (ophthalmopegia, ataxia and confusion)
- New-onset (starting >24h after randomization) severe hypoglycemia (< 40 mg/dL)
- Anaphylactic reactions presumed to be caused by the study treatment

1.8.7.1.5 Additional lab and clinical assessments for the SALADIN nested substudy

- Assessments on urine collections from each ICU day (Figure 1), until the day the urinary catheter is removed, bladder irrigation is initiated, renal replacement therapy with net ultrafiltration begins, or the patient is discharged from the ICU, whichever occurs first:
  - Urine osmolality, to calculate solute-free water clearance
  - Urine sodium, to calculate sodium balance, fractional excretion of sodium, electrolyte-free water clearance
  - Urine chloride, to calculate chloride balance
  - Urine potassium, to calculate electrolyte-free water clearance
  - Urine urea, to calculate fractional excretion of urea and compare solute-free and electrolye-free water clearance
  - Urine creatinine, to calculate fractional excretion of sodium and fractional excretion of urea
  - Urine volume, to calculate solute-free water clearance, electrolyte-free water clearance, sodium and chloride balance
- Concomitant medication: administration of oral loop diuretics (furosemide (Lasix®, bumetadine (Burinex®)), oral thiazide diuretics (chloortalidon (Hygroton®), indapamide (Fludex®) or oral or intravenous potassium-sparing diuretics (spironolacton (Aldactone® and Soldactone®), including combination preparations. Collected as yes/no variables per type (loop, thiazide, potassium sparing).
- Whole blood and plasma values assessed in the central lab within the standard of care
  - Hemoglobin level, and plasma osmolality within a window of 6 hours before or after admission, and on the routine morning assessment of each ICU day, including the time of sampling. ICU days start at 8 AM, but routine blood samples are often collected earlier. Regardless of timing, morning samples count toward the ICU day beginning at 8 AM.
- Daily body weight, to correlate with daily fluid balance, measured throughout the ICU day at a time most convenient for the nursing team.
- Bioelectrical Impedance Analysis. Measurements will be conducted at least once every three ICU days starting from the day of randomization.
  - Total Body Water (TBW), Intracellular Water (ICW), and Extracellular Water (ECW) in liters and percentages, and ECW/ICW ratio
  - Intravascular (IVF) and extravascular (EVF) fluid, and EVF/IVF ratio
  - Volume excess (VE)
  - Fat-Free Mass (FFM, kg and %), Fat-Free Mass Hydration (FFMH, %), and Fat Mass (FM, kg and %)
  - Protein mass (kg), Mineral mass (kg), Bone mass (kg), Muscle mass (kg)
  - Resting Metabolic Rate (RMR), Glycogen deposits (g)
  - Phase angle and Malnutrition Index

1.8.7.2 Follow up phase and variables to be collected at end-of-study visit

Follow-up for the primary outcome will be until death or 90 days after ICU admission, whichever comes first. During the end-of-study visit, the following assessments will be recorded (+ 10 days):

- Day of discharge from the ICU
- Survival status and destination at discharge from the ICU: hospital ward, step-down unit, rehabilitation or long-term facility, home or place of residence before hospital admission, residential care facility, palliative care, other

- Day of discharge from the hospital
- Survival status and destination at discharge from the hospital: rehabilitation or long-term facility, home or place of residence before hospital admission, residential care facility (new onset), palliative care, other
  If a patient is transferred to another hospital, the additional days spent in that hospital are included in the total hospital length of stay (LOS) for the study endpoint. However, if the patient is discharged to a rehabilitation (revalidation) department within the hospital, these days are not counted as part of the hospital length of stay.
- Days alive and without life support at day 90 after ICU admission
- Days alive and out of hospital at day 90 after ICU admission
- Ventilation-free days. Mechanical ventilation (invasive and non-invasive) days are counted if discharged to another ICU, but not to another ward, facility or home.
- Renal replacement-free days. Use of renal replacement therapy is counted after ICU discharge. Periods with up to 3 days between intermittent hemodialysis are counted as days with RRT, e.g. if a patient received IHD on day 1, did not receive IHD on days 2–4, and received IHD again on day 5, the patient is considered to have been on RRT for the entire period from day 1 through day 5.

1.8.8 Withdrawal criteria

1.8.8.1 Discontinuation of study intervention at the choice of the investigator

1.8.8.1.1 Discontinuation of maintenance fluids according to study arm

Discontinuation of maintenance fluids within the protocol is further described under Section 1.9.

The following discontinuations are allowed within the study protocol:

- No need for maintenance solutions, a decision that is taken at the discretion of the treating physician.
  - Sufficient water and electrolytes through other sources
    - Enteral or parenteral nutrition,
    - Blood products
    - Fluid creep
  - Reasons to restrict fluid administration
    - (fear of) fluid overload, fluid retention
    - Organ-specific reason: e.g. heart or liver failure
    - Need for water restriction (e.g. ARDS, SIADH).

  In the cases mentioned above, no off-study maintenance fluids should be prescribed.
- Need for a specific type of maintenance fluids due to a new-onset contraindication to one of the study-fluids, a decision that is taken at the discretion of the treating physician. Five reasons are authorized to switch to off-study maintenance fluids.
  - New-onset neurological contra-indication to study maintenance fluids, i.e. risk of- brain edema, e.g. traumatic brain injury, subarachnoidal hemorrhage, hemorrhagic or ischemic stroke, meningitis or encephalitis,…
  - Hypernatremia, where it is accepted that off-study maintenance solutions are prescribed that are completely sodium-free (at the discretion of the treating physician).
  - Hyponatremia, where it is accepted that off-study isotonic maintenance solutions are prescribed (at the discretion of the treating physician)
  - Extreme hyperglycemia. Mostly, hyperglycemias will be treated in the ICU with insuline without altering maintenance prescription, but the treating clinician can decide that some instances of hyperglycemia are just too high to temporarily warrant further treatment with glucose-containing study fluids.
  - Clinical refeeding syndrome

  The prescription of off-study maintenance fluid outside of the situations above are treated as **protocol violations**.
  From the moment the indication for a specific non-study maintenance fluid is no longer present, study fluids are resumed according to the randomized study arm.

1.8.8.1.2 Discontinuation of fluid creep according to study arm

Since medications are often dissolved in glucose 5% as the standard-of-care in all clinical situations, it will be very rarely needed to change the composition of fluid creep, even in case of dysnatremias, dysglycemias etc. This situation is best discussed as soon as possible with a member of the study team. Yet, it is at the discretion of the treating physician to stop the study treatment. The reason should be recorded in the patient's medical records and be reported on the appropriate (e)CRF.

We will have a CRUSADERS trial hotline to enable discussion between 8AM and 10PM between the clinicians caring for trial participants and the CRUSADERS trial team regarding protocol related issues.

1.8.8.2 Withdrawal of consent (discontinuation of study participation)

The patient may withdraw consent at any time during the study, without providing any explanation. For participants who are unable to provide written consent, the proxy who granted consent on their behalf may withdraw it at any time. Upon withdrawal of consent, all study-prescribed maintenance fluids will be discontinued. Composition of subsequent maintenance fluids will be prescribed at the discretion of the treating physician. Once any previously dissolved medications have been administered, subsequent medications will be prepared and administered in accordance with the hospital's standard procedures.

To limit the amount of missing data, we will collect as much data as possible from each participant. Therefore, if possible, the investigator will ask the participant or the proxy to which extent the withdrawal includes:
• receiving the trial intervention only (allowing for all data registration and follow-up)
OR
• receiving the trial intervention AND further registration of daily data and/or follow-up

Only the participant can demand deletion of already registered data and only if the participant did not consent previously. If so, the data will be deleted, and a new participant will be enrolled to obtain the full sample size.

The details of withdrawal should be clearly documented in the patient's medical records and in the (e)CRF.

1.8.8.3 Loss to follow-up

After a patient is discharged from the hospital, every effort should be made to contact them to collect the necessary data for the follow-up phase and the End of study visit on Day 90 (+ 10 days).

For the End of study visit, a study team member will call the patient to confirm the study-specific assessments. If the patient or their relatives cannot be reached, two additional follow-up attempts will be made on different calendar days. If the patient has been transferred to another institution, the treating team at that institution will be contacted.

A patient is classified as lost to follow-up after three documented attempts to reach them, with the date of the third attempt recorded in the eCRF. If the patient had been discharged to their home or pre-admission residence, they are classified as a survivor. In all other cases, survival status is recorded as missing data.

1.8.9 Discharge to another ICU

Participants transferred to another ICU will continue to receive study treatments when the ICU is an active CRUSADERS trial site, provided the study fluid is still available in the department (see Randomization Schedule).
If the patient is discharged to an ICU that is not an active CRUSADERS trial site, the days of stay in that ICU are counted as ICU days for the length of stay endpoint although study treatments are stopped.

1.8.10 End of study

End of study is 90 days after admission of the last patient to the ICU. A summary of the results of the study will be submitted to the CA/IEC (via CTIS) within 1 year from the end of the study, irrespective of the outcome of the study.

1.9 STUDY TREATMENTS

1.9.1 Name and description of intervention

All the used fluids are authorised medicinal products for every indication used in the study, either for maintenance fluid therapy, for keeping lines open and for dissolving approved medications. As such,

nothing is prescribed during the study that is not being prescribed in current practice in different hospitals all over the world. This classifies the study as a **low-intervention trial.**

Fluid creep: all medications used in the ICU can be dissolved in both glucose 5% and in NaCl 0.9% if stated in their SmPC, an overview of which has been published by Van Regenmortel et al.(2) Exceptions are dissolved in their mandatory solution. Currently, amoxicilline-clavulanate, somatostatin, diphantoine and acyclovir are always dissolved in NaCl 0.9% and noradrenaline and amiodarone are always dissolved in glucose 5%. Knowledge of these six medications is part of study-specific training and is displayed on a poster in the medication preparation room.

Maintenance fluid therapy: during study-specific training, clinicians and researchers will be trained to acknowledge the following aspects:

- The inclusion of glucose in maintenance fluids lacks robust scientific evidence, and clinicians' perspectives on its necessity vary globally, often influenced by local or personal practices. To ensure the trial reflects real-world clinical scenarios, we designed the CRUSADERS trial to avoid using less commonly employed solutions such as PlasmaLyte in glucose 5% or NaCl 0.9% in glucose 5% as comparators. Instead, we opted for the widely practiced standard of using isotonic balanced solutions without glucose. However, it is recognized that in certain cases, clinicians who believe this is relevant may choose to add glucose to the treatment regimen, particularly when patients are unable to tolerate enteral feeding, to prevent hypoglycemia or starvation ketosis. Therefore, during the study, if the treating clinician has concerns about starvation ketosis or hypoglycemia **in specific cases, 50% glucose may be administered at a low rate as part of the treatment**.
- As opposed to the composition of maintenance fluids, which is the object of the study, **the *indication* for maintenance fluids, and the *prescribed volume*, is always at the discretion of the treating physician**.
    - Maintenance fluids can be (temporarily) stopped when sufficient water and electrolytes are administered through other sources (e.g. enteral nutrition) or when restriction of fluid administration is needed. See also Section 1.8.8.1.1 Discontinuation of maintenance fluids according to study arm and Figure 6.
    - Switching of maintenance fluids to prescribe non-study maintenance fluids is allowed in certain conditions that are specified in Section 1.8.8.1.1 Discontinuation of maintenance fluids according to study arm. Prescription policies of maintenance fluids in the CRUSADERS trial are summarized in Figure 6 and are the subjects of study-specific training.
- Maintenance fluids, which address patients' daily water and electrolyte needs, **differ from replacement fluids**, which compensate for past and ongoing fluid losses. The rate and sodium or chloride content of additional fluids to manage such losses (e.g., due to drains, fever, hypernatremia, or specific conditions like pancreatitis or burns) are determined at the discretion of the treating physician. If both maintenance and replacement fluids are required and if the treating physician considers both study treatments appropriate for replacement, the study fluid can be increased accordingly. If a specific fluid is needed for replacement, or if the required volumes are considered too high to safely treat the patient with blinded study fluids alone, it should be prescribed separately.

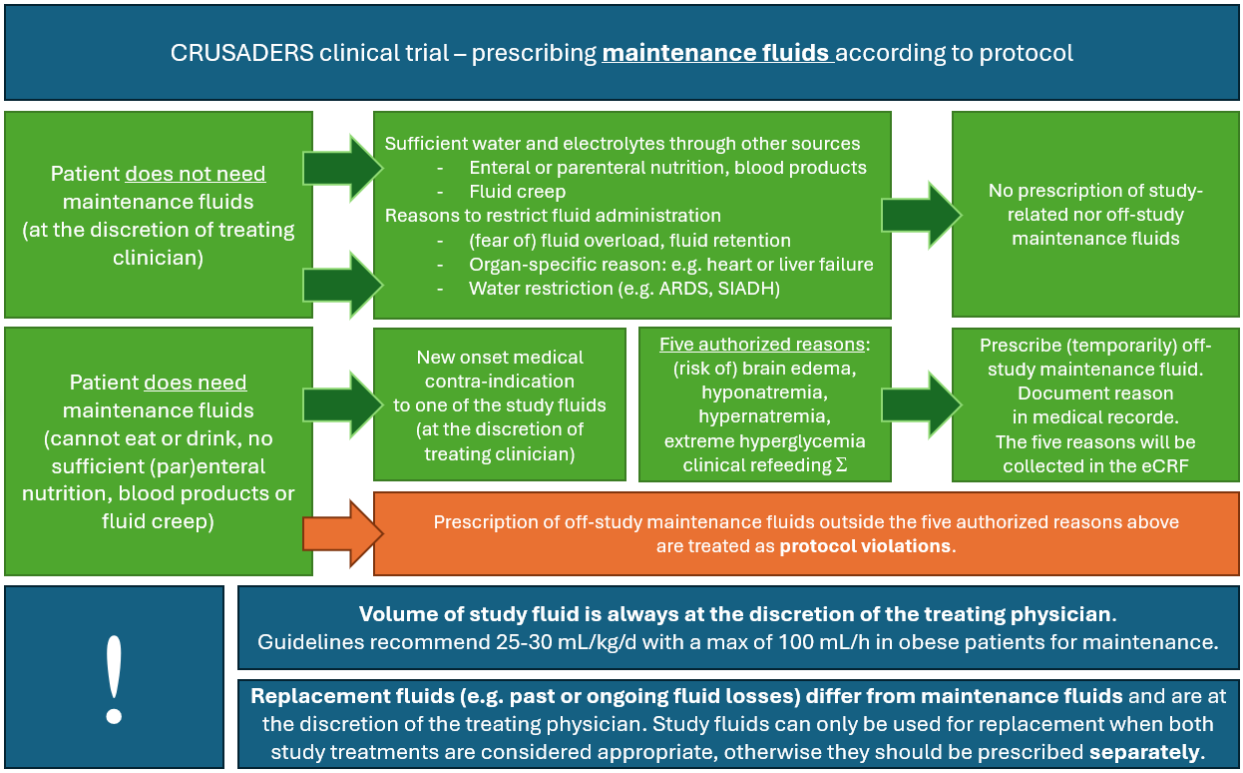


Figure 6: Guidance on prescribing maintenance fluids

1.9.1.1 Intervention: sodium chloride reduction strategy, the NaCl-poor arm

Fluid creep:
- Medications, including concentrated electrolytes, are dissolved in **glucose 5%** except when another solvent is mandatory according to the responsible pharmacist.
- Infusions to keep intravascular lines open are **glucose 5%** with the exception of arterial lines to avoid the false detection of hyperglycemia on blood gas analysis.

Maintenance fluids:
- Type: maintenance fluid is **NaCl 0.3% in glucose 3.3%.** Potassium chloride or potassium phosphate can be added (or administered separately) at the discretion of the treating physician whenever necessary.
- Rate: at the discretion of the treating physician, typically 25-30 ml/kg of body weight with a maximum of 100 ml/hour, accounting for concomitant fluid sources such as nutrition and fluid creep. It is allowed to prescribe a higher volume of study maintenance fluids to include replacement if both study fluids are considered appropriate.

1.9.1.2 Control: isotonic fluid strategy, the NaCl-rich arm

Fluid creep:
- Medications, including concentrated electrolytes, are dissolved in **NaCl 0.9%** except when another solvent is mandatory according to the responsible pharmacist.
- All infusions to keep lines open are **NaCl 0.9%**.

Maintenance fluids:
- Type: Maintenance fluid is **PlasmaLyte**. Potassium chloride or potassium phosphate can be added (or administered separately) whenever deemed necessary.
- Rate: at the discretion of the treating physician, typically 25-30 ml/kg of body weight with a maximum of 100 ml/hour, accounting for concomitant fluid sources such as nutrition and fluid creep. It is allowed to prescribe a higher volume of study maintenance fluids to include replacement if both study fluids are considered appropriate.

1.9.1.3 Duration of the intervention

The treatment phase, during which the intervention takes place, begins as soon as possible after randomization. Maintenance fluids and line patency fluids must be initiated or replace current

maintenance within two hours, while medications are first dissolved in the study treatment at the next scheduled administration requiring dissolution.

Treatment continues until the patient is discharged from the ICU or until the study-specific fluid is no longer available in the department (according to the Randomization Schedule at least 28 days after randomization).

If the patient is readmitted to the ICU while the study fluid corresponding to their randomized letter (as per the Randomization Schedule) is still available in the department, the study treatment should resume according to the assigned study arm.

1.9.2 Legal status of the intervention

All study fluids are licensed for use in Belgium and worldwide in all indications included in the protocol.

1.9.3 Drug storage and supply

All fluids will be packaged in a manner which is distinguishable to research sites so must be received by and handled only by unblinded pharmacy personnel until distinguishing features are obliterated at the point of issue to blinded caregivers in the ICU department.

- Supply details
  - The investigational fluids will be supplied by Baxter Healthcare in their usual Viaflo bags.
- Storage requirements
  - Upon receipt, the pharmacy will store the fluids under standard conditions appropriate for these products, in accordance with their routine handling procedures for maintenance solutions.
- Preparation and distribution
  - The unblinded pharmacists, independently delegated by the principal investigator (PI), will label the study fluids with their respective randomization codes and deliver them to the ICU for administration to study participants. They will manage the supply proactively, ensuring that sufficient fluids are available at all times, including nights and weekends, without the need for specific ordering or prescriptions
- Storage after dispensing
  - The prepared solutions will be stored in the ICU department under the conditions specified by the product requirements and in clearly labeled, dedicated study-specific storage areas. Medications dissolved in the study treatment will be handled and stored under standard conditions, as per routine clinical practice.
- Accountability and destruction
  - All unused or remaining fluids will be accounted for and destroyed by the pharmacy after the conclusion of the study. The destruction process will comply with local regulatory requirements and pharmacy protocols to ensure proper disposal of investigational products.

1.9.4 Preparation and labelling

All study fluids in their four volumes per arm (50 mL, 100 mL, 250 mL, 500 mL) are labelled with the study name and the randomization code letter (see Randomization) by the responsible unblinded pharmacist. The blinding process occurs prior to the fluids being delivered to the ICU, ensuring that in the ICU, only blinded fluids are present.

In the CRUSADERS trial, the Investigational Medicinal Products (IMPs) can be classified into three categories regarding the handling of the labelling: (1) Maintenance fluids and line patency fluids (2) Study fluid bags to which medications are added and (3) Diluent fluids drawn from the study fluid bag for medication preparation in a separate receptacle, such as a syringe pump.

1. Maintenance fluids and line patency fluids will already be labeled with the study name and randomization letter by the unblinded pharmacist. The nurse adds a standard label with the patient identifier before administration. If other medications such as concentrated electrolytes or vitamins are added to the fluid, this will appear on the label.
2. Study fluid bags to which medications are added will be pre-labeled with the study name and randomization code letter by the unblinded pharmacist. The nurse will then add the patient identifier label before administration. This label follows the standard procedure, which may, depending on the site, also display the standard diluent used. Modifying this standard label would interfere with the primary labeling system for medications, which is essential for preventing medication errors. Reprogramming the Electronic Patient File (EPF) for each individual medication is unfeasible and requesting the nursing team to create ad hoc written labels could introduce additional errors and unacceptable risks. By retaining the standard label on the fluid bag, the original medication labeling system remains the primary focus, ensuring patient safety through the accurate identification of the active medication, which is critical for correct dosing and administration.
3. Diluent fluids drawn from the study fluid bag for medication preparation in a separate receptacle, such as a syringe pump will be labelled with a sticker with the name of the trial. The nurse will also add the patient identifier label before administration. This label follows the standard procedure, which may, depending on the site, also display the standard diluent used. Modifying this standard label would interfere with the primary labeling system for medications, which is essential for preventing medication errors. Reprogramming the Electronic Patient File (EPF) for each individual medication is unfeasible and requesting the nursing team to create ad hoc written labels could introduce additional errors and unacceptable risks. By retaining the standard label on the fluid bag, the original medication labeling system remains the primary focus, ensuring patient safety through the accurate identification of the active medication, which is critical for correct dosing and administration.

1.9.5 Dosage schedules

Dosage of the maintenance fluids are at the discretion of the treating clinician. Dosing is not a part of the intervention.

The medications are dissolved in volumes specified by the standard-of-care and stated per-medication in the electronic prescription tool in HIX, Chipsoft software.

1.9.6 Assessment of compliance (if applicable)

Nursing teams will receive extensive training in study procedures. Maintenance solutions will be prescribed and recorded as CRUSADERS study fluid in the (electronic) medical records together with all other prescribed and administered intravenous fluids so that compliance can be monitored. The amount of study fluids used for fluid creep (line patency volumes and medication diluents) will be electronically entered into the Electronic Patient File (EPF) or kept on paper as part of the source documents by the nurse retrieving them from the medication preparation area in the department.

Remote monitoring will specifically track the volumes of study fluids and intervene if they deviate from the expected percentages.

1.9.7 Concomitant therapy

All concomitant therapy is allowed without exceptions during the study and at the discretion of the treating clinician.
In the SALADIN nested substudy, daily use of oral loop and thiazide diuretics and oral and intravenous potassium-sparing diuretics will be recorded as yes/no variables.

1.10 SAFETY RECORDING AND REPORTING

Definitions:

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the study in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which <u>may</u> be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

	Findings	Recording	Reporting
SAE	Any SAE	• Standard medical records • Some captured as safety variables in eCRF (AKI, mortality, LOS)	No (common in ICU)
Adverse reactions	• Local irritation, local pain, extravasation, pruritus, phlebitis and thrombophlebitis (all study fluids). • Urticaria (all study fluids) • Chills or pyrexia (PlasmaLyte) • Metabolic acidosis (NaCl 0.9%) and alkalosis (PlasmaLyte) • Hypokalemia (glucose 5%) and hyperkalemia (NaCl 0.9%) • Mild dysnatremia and dyschloremias • Cardiac arythmias (PlasmaLyte) • Paralytic ileus (PlasmaLyte) • Diarrhea (PlasmaLyte)	• Standard medical records	No
Adverse reactions	• Hyperglycemia (attributable hyperglycemia outside classic stress hyperglycemia in the ICU is rare) (Glucose 5%) • Electrolyte disorders, such as hyponatremia (glucose 5%), hypernatremia (NaCl 0.9% and PlasmaLyte) and hyperchloremia (NaCl 0.9%) • Symptomatic or asymptomatic fluid and sodium retention, recorded in the form of diuretic use and daily and cumulative fluid balance	• Standard medical records • Captured as safety variables in eCRF	No
Serious adverse reactions	• New onset (>48h) symptomatic severe hypoNa (<125) • Central pontine myelinolysis (CT, MRI) after new onset hypoNa • New onset (>48h) symptomatic severe hyperNa (>155) (seizures) • New onset (>24h) severe hypoglycemia (<40 mg/dL) • New onset (>48h) clinical refeeding Σ • New onset (>48h) Wernicke encephalopathy • New onset (>48h) starvation ketosis • Anaphylactic reactions	• Standard medical records • Captured as SAR in eCRF	<72h
SUSAR	Any SUSAR	• Standard medical records • eCRF	<24h

An overview of the recording and reporting of SAE's, SAR's and SUSAR's.

1.10.1 Recording of safety findings in function of the available evidence

1.10.1.1 Recording of Serious adverse events

The CRUSADERS patient population is a seriously ill group and is expected to have a very high proportion of (serious) adverse events. It is therefore not feasible, nor meaningful to record and report all adverse events in the eCRF. Recording of every SAE in the medical records is seen as part of standard of care patient file management.

The serious adverse events relevant to the study (typically mortality, ICU and hospital length of stay, onset and duration of organ support) are all captured by the outcome parameters and thus recorded in the medical file and in the eCRF.

1.10.1.2 Recording of Serious adverse reactions and SUSARs

The study fluids for maintenance and fluid creep, both in the NaCl-poor and the NaCl-rich study arms, are routinely used on a daily basis in critically ill patients worldwide within their approved label. Therefore, diagnosing and treating their (well-known) adverse reactions are part of the daily work of ICU physicians. The chance of *unknown* adverse reactions is close to none and most of them will be related to the dose (which is at the discretion of the treating physician) rather than the type.

The CRUSADERS-trial therefore adopts the following, **trapped procedure for recording** the (S)ARs that are stated in the SmPc of the different fluids used in the study.

- Well-known adverse reactions to be recorded in the medical record, but <u>not in the eCRF</u>, in view of their on-label use, different causes outside the study treatment and the fact clinicians working in the department of ICU are well-trained to deal with each of these situations appropriately

  - Local irritation, local pain, extravasation, pruritus, phlebitis and thrombophlebitis (sometimes: >1/1000 - <1/100) (all study fluids).

- Urticaria (rare: >1/10.000 - <1/1000 to extremely rare: <1/10.000) (all study fluids, although rarely attributable to these fluids in the ICU))
- Chills or pyrexia (sometimes encountered in patients who are allergic to maïze) (frequency unknown) (PlasmaLyte, although rarely attributable to this fluid in the ICU)
- Metabolic acidosis (NaCl 0.9%) and alkalosis (PlasmaLyte)
- Hypokalemia (glucose 5%, NaCl 0.3% in glucose 3.3%) and hyperkalemia (NaCl 0.9%, PlasmaLyte)
- Cardiac arythmias and palpitations (PlasmaLyte, although rarely attributable to this fluid in the ICU)

- The following well-known adverse reactions to be recorded in the medical records and are collected as safety variables in the eCRF

  - Hyperglycemia due to the solutions' glucose content (attributable hyperglycemia outside classic stress hyperglycemia in the ICU is rare) (>1/10.000 - <1/1000 to extremely rare: <1/10.000) (glucose 5%, NaCl 0.3% in glucose 3.3%)
  - Electrolyte disorders, such as hyponatremia (glucose 5%, NaCl 0.3% in glucose 3.3%), hypernatremia (NaCl 0.9% and PlasmaLyte) and hyperchloremia (NaCl 0.9%) (frequency unknown)
  - Fluid and sodium retention (frequency unknown), recorded in this trial in the form of diuretic use and daily and cumulative fluid balance

- Well-known (serious) adverse reactions to be recorded in the medical records by the clinical team, and as SARs in the eCRF by the study team:
  - New-onset (starting > 48h after randomization) **severe hyponatremia (<125 mmol/L) with seizures or profound lethargy unexplained by sedation or other disease.**
  - New-onset (starting > 48h after randomization) **severe hypernatremia (>155 mmol/L) with seizures or profound lethargy unexplained by sedation or other disease.**
  - New-onset (starting >24h after randomization) **severe hypoglycemia (< 40 mg/dL)**
  - New-onset **central pontine myelinolysis** (symptoms starting > 48h after randomization), confirmed on MRI within 90 days of admission
  - New-onset (starting > 24h after randomization) **clinical refeeding syndrome**, defined as severe hypophospatemia < 1 mg/dL or < 0.32 mmol/L + hypokalemia < 3 mmol/L + clinical picture with symptoms such as fluid retention, edema, extreme muscle weakness, cardiac arrythmias, heart failure, respiratory failure, seizures or a combination of the above.
  - New onset (starting > 24h after randomization) **Wernicke encephalopathy** defined by the triad of ophthalmopegia, ataxia and confusion.
  - **Anaphylactic reactions presumed to be caused by the study treatment**, defined as urticaria and at least one of following: hemodynamic instability, increased airway resistance, stridor or bronchospasm treated with bronchodilators.

- SUSARs, to be recorded in the medical records and in the eCRF

1.10.2 Expedited reporting of SAEs, SUSARs

1.10.2.1 Serious adverse events

The CRUSADERS patient population is a seriously ill group and is expected to have a very high proportion of (serious) adverse events. Even mortality rates can be high, and in some of the studied reasons for admission higher than 50%, with the (on-label) intervention playing a small or indirect role. It is therefore **not meaningful to report** any serious adverse events, including death.

1.10.2.2 Serious adverse reactions

A similar **trapped procedure for reporting** is applied:

- Well-known (serious) adverse reactions, not to be reported, as their cause is often multifactorial (and impossible to attritbute to the intervention alone) and their detection and treatment is routine care in an intensive care department.

  - Local irritation, local pain, extravasation, pruritus, phlebitis and thrombophlebitis (all study fluids).
  - Urticaria (all study fluids)
  - Chills or pyrexia (PlasmaLyte)
  - Metabolic acidosis (NaCl 0.9%) or alkalosis (PlasmaLyte)
  - Hypokalemia (glucose 5%, NaCl 0.3% in glucose 3.3%) or hyperkalemia (NaCl 0.9%, PlasmaLyte)
  - Cardiac arythmias, palpitations (PlasmaLyte)
  - Hyperglycemia or mild hypoglycemia (>40 mg/dL) (glucose-containing solutions)
  - Mild or moderate dysnatremia or asymptomatic severy dysnatremias or any dyschloremia (all study fluids)
  - Symptomatic or asymptomatic fluid retention

- Serious adverse reactions to be reported by the local study team using a dedicated part of the eCRF (REDCap) **within 72 hours** of the research staff becoming aware of the event:

  - New-onset (starting > 48h after randomization) severe hyponatremia (<125 mmol/L) with seizures or profound lethargy unexplained by sedation or other disease.

  - New-onset (starting > 48h after randomization) severe hypernatremia (>155 mmol/L) with seizures or profound lethargy unexplained by sedation or other disease.

  - New-onset (starting >24h after randomization) severe hypoglycemia (< 40 mg/dL)

  - New-onset central pontine myelinolysis (symptoms starting > 48h after randomization), confirmed on MRI within 90 days of admission

  - New-onset (starting > 24h after randomization) clinical refeeding syndrome, defined as severe hypophospatemia < 1 mg/dL or < 0.32 mmol/L + hypokalemia < 3 mmol/L + clinical picture with symptoms such as fluid retention, edema, extreme muscle weakness, cardiac arrythmias, heart failure, respiratory failure, seizures or a combination of the above.

  - New onset (starting > 24h after randomization) Wernicke encephalopathy defined by the triad of ophthalmopegia, ataxia and confusion.

  - Anaphylactic reactions presumed to be caused by the study treatment, defined as urticaria and at least one of following: hemodynamic instability, increased airway resistance, stridor or bronchospasm treated with bronchodilators.

  For each of the above SAEs the following information will be collected:

  - Full details in medical terms and case description, including details on the administration of non-study fluids
  - Event duration (start and end dates, if applicable)
  - Action taken
  - Outcome
  - Seriousness criteria
  - Causality (i.e. relatedness to study drug), in the opinion of the investigator
  - Whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be notified to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

→ Rationale: The reason a 72-hour window is sufficient is that the study fluids, both in the NaCl-poor and the NaCl-rich study arms, are routinely used on a daily basis in critically ill patients worldwide within their approved label. Therefore, diagnosing and treating their (well-known) adverse reactions are part of the daily work of ICU physician.

1.10.2.3 SUSARS

All SUSARs occurring from the time of start of study treatment until 72h post cessation of study treatment must be recorded on the SUSAR Form in the eCRF and e-mailed to the Sponsor **within 24 hours** of the the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form to be posted to the Sponsor and a copy to be retained on site.

For each SUSAR the following information will be collected:

- Full details in medical terms and case description, including details on the administration of non-study fluids
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to study drug), in the opinion of the investigator

Any change of condition or other follow-up information should be notified to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SUSARs will be subject to expedited reporting to the EMA. The Sponsor will inform regulatory authorities and the Marketing Authorisation Holder of SUSARs within the required expedited reporting timescales. In addition, we will report the abovementioned, to-be-reported SARs defined in 1.10.1.2 and SUSARS in the final trial report and the results of the trial will be reported on EudraCT.

Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs which are required to continue being reported according to the protocol for regulatory purposes. The ICF includes a section explaining this to the participant.

1.10.3 Responsibilities

Principal Investigator (PI):

- Checking for AEs and ARs during and within 48h after treatment:
- Using medical judgement in assigning seriousness, causality and expectedness using the Reference Safety Information approved for the study.
- Ensuring that the predefined SARs and SUSARs reported to the Sponsor within 72 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that predefined SARs and SUSARs are shared with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

- Clinical oversight of the safety of patients participating in the study, including an ongoing review of the risk / benefit. The CI reviews a line listing of predefined SARs on a monthly basis.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of all SUSARs.

- Review of specific SAEs and SARs in accordance with the study risk assessment and protocol as detailed in the Trial Monitoring Plan.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

- Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the study protocol onto a safety database.
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the study (Data and Safety Monitoring Board (DSMB) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
- Expedited reporting of SUSARs to the Eudravigilance database (EVWEB).
- Notifying Investigators of SUSARs that occur within the study.
- The unblinding of a participant for the purpose of expedited SUSAR reporting
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the study.
- Preparing standard tables and other relevant information for the ASR in collaboration with the CI and ensuring timely submission to the Eudravigilance database.

Trial Steering Committee (TSC):

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the study. The TSC must also include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC will monitor study progress, conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, and ultimately carries the responsibility for deciding whether a study needs to be stopped on grounds of safety or efficacy.

The TSC will meet **2 times per year the first year** and **once a year after that**. The TSC is composed of the CI, the study statistician, the trial manager, at least three independent experts, a representative of participating centres, one patient or member of the public, one representative of the sponsor and one representative of the funder.

Data and Safety Monitoring Board (DSMB):

A Data and Safety Monitoring Board is a group of independent experts external to a study assessing the progress, safety data and, if needed critical efficacy endpoints of a clinical study. In order to do so, a DSMB may review unblinded study information (on a patient level or treatment group level) during the conduct of the study. Based on its review, the DSMB provides the Sponsor with recommendations regarding study modification, continuation or termination. The DSMB of the CRUSADERS trial consists of a **chairperson, two experts who are both ICU clinicians and ICU clinical researchers and an independent statistics/clinical research expert.**

The DSMB reviews a line listing of predefined SARs (new-onset severe symptomatic hyponatremia, severe hypernatremia, central pontine myelinolysis and clinical refeeding syndrome) on a 1 yearly basis. The total numbers of that SARs above and SUSARs are sent to the DSMB Chair per six months – in order to expedite a safety review if more SARs are being seen than would be expected.

1.10.4 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the regulatory authorities through the CTIS of the measures taken and the circumstances giving rise to those measures.

1.10.5 The type and duration of the follow-up of subjects after adverse events

All the abovementioned SAR's will be followed up by the treating team until safe to transfer to a step-down treating team.

Any SUSAR related to a study arm will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

1.11 STATISTICS AND DATA ANALYSIS

1.11.1 Sample size calculation

1.11.1.1 Prior literature

- Current knowledge on the proportion of fluid creep and maintenance fluids relative to total fluid intake:

Van Regenmortel et al (2018)(1): Fluid creep: mean 757 mL, median 645 (IQR 308-1039) mL = 33% of a mean total volume of 2.3L (SD 1.3L) per ICU day and a median of 2.3L (IQR 1.4—3.0) per ICU day. Combined volume of maintenance and replacement fluids: mean 574, median 334 (IQR 150-894) mL = 25% of a mean total volume of 2.3L (SD 1.3L) per ICU day and a median of 2.3L (IQR 1.4—3.0) per ICU day. (Total fluids include enteral nutrition (mean 441ml, median 0 (IQR 0-995).)

Magee et al (2018)(21): creep accounts for a median volume of 3.5L (IQR 3-11L), which is median 63% (IQR 43-83%) of total fluid volume over an unclear amount of time (max. 7 days). Total fluids do not include enteral nutrition.

Bihari et al (2018)(19): drug infusions 420 ml (IQR 210-700) on a total of 2.1L (IQR 1.6-2.7L) including enteral feeds (1.1L IQR 685-1440). Maintenance 1.1L (0.7-1.4L).

It should be acknowledged that not all fluid creep can be chosen as various medications are already predissolved and that distinguishing maintenance from replacement fluids is impossible from currently available literature.

- Current knowledge on the impact of sodium burdens on fluid balance:

MIHMoSA study (2017)(3): mean volume 1.7L. Sodium 154/54 =267/94 mmol/48h. Fluid balance after 48h 3060mL vs 3655 mL = Delta 595 mL. No other fluid sources.

TOPMAST study (2019)(4): mean volume 2.7L. Mean daily sodium administration (including non-study fluid) 154/54 = 8.4/4.6g per day. Fluid balance after 72h 4.5L/3.1L = Delta 1.4L. Median 0-1000 and 0-500mL of resuscitation fluids.

DEMANDS study (2024)(22): open-label RCT in which 100 patients with septic shock received dextrose 5% or NaCl 0.9% for maintenance and creep (+/- 6L in each arm in 72h). Fluid balance 2.06L more positive in the saline arm (95%CI 1.35-2.63L)

- Current knowledge on the impact of fluid balance on mortality

SOAP study, Vincent et al (2005)(5): cumulative fluid balance OR for mortality 1.1 (95%CI 1.0-1.1) per liter increase. Caveat: fluid balance as a marker of illness severity versus iatrogenic fluid overload!

- Current knowledge on the impact of sodium reduction on organ failure and mortality

Magee (2018)(21): choice of creep fluid significantly associated with AKI (34% saline, 25% G5%, p0.035) but not significant when corrected for baseline (saline bolus, serum Na, total medication diluent volume, weight, APACHE II). Diluent group shows a significant association with hyperchloremia OR 0.5 (95% CI 0.26-0.83). No impact on incidence of hypoNa, hyperglycemia, insulin use.

DEMANDS study (2024): ventilator-free days 18 (IQR 0-26) in the dextrose arm, 12 (IQR 0-24) in the NaCl 0.9% arm (p=0.167).

DEMANDS study (2024): 28 days mortality 32% in the dextrose arm, 42% in the NaCl 0.9% arm. Absolute difference 10% (9-28%) (p=0.1).

- Current knowledge on the impact of chloride reduction on organ failure/mortality.

Semler (2018)(44): balanced solutions (98 mmol/L of chloride) (median 1000mL IQR 0-3210mL between admission and hospital discharge) compared to NaCl 0.9% (154 mmol/L) (median 1020mL IQR 0-3500mL between admission and hospital discharge) was associated with significantly higher incidence of major kidney events at day 30.

A meta-analysis by Zampieri et al.(16) showed that there is a high probability (90%) that chloride-poor resuscitation fluids slightly reduce mortality (0.4%) compared to a chloride-rich strategy.

It has to be noted that the chloride-reduction of switching maintenance fluids and fluid creep from isotonic solutions to hypotonic solutions is much larger than switching resuscitation fluids from NaCl 0.9% to balanced isotonic fluids.(1)

1.11.1.2 Sample size calculation

The sample size calculation was based on the data of the ZAS-sites (where part of the trial will be conducted) and the DEMANDS trial where a 24% relative reduction in mortality and an increase of 6 days in median ventilator-free days was reported in a population of patients with septic shock. The DAWOLS distribution was simulated using Yehya et al. (2019).(45) Mortality is simulated according to a Bernouilli distribution and number of days of life support among survivors according to an exponential distribution. We assumed that 15% of patients would die within 90 days while receiving life support, and survivors would receive an average of 7 days of life support, this averages to 70.6 days alive without life support for the NaCl-rich arm. If we estimate that the NaCl-poor arm would reduce 90-day mortality by a 16% relative reduction and yield a 27% decrease in days receiving life support for survivors, this corresponds to an average of 74.2 days alive without live support in the NaCl-poor arm. Based on this, we estimate that **with a power of 80% and a two-sided alpha of 5%, 640 patients are needed** to detect the absolute between-group difference of 3.6 days alive without life support**, including a dropout of 15%**. These results are based on 3000 simulations using a Mann Whitney U test.

1.11.2 Planned recruitment rate

Based on the data of ZNA Campus Stuivenberg (2021-2022, currently moved to ZAS Campus Cadix) and of the Antwerp University Hospital (UZA), we conservatively predict that 40% of patients have an ICU stay of three days or more, and 18.5% would meet all inclusion and exclusion criteria and would provide written informed consent. Running the trial for two and a half years in ZAS Palfijn (± 37 patients per year), in UZA, ZAS Cadix and ZAS Middelheim (± 74 patients per year each) would lead to an estimated recruitment of 640 patients. Final numbers will be adjusted based on actual recruitment rates, and sites are not restricted to a set number of patients.

1.11.3 Statistical analysis plan

The complete details of the statistical analysis will be provided in a separate statistical analysis plan, which will be finalized prior to the data lock.

1.11.3.1 Summary of baseline data and flow of patients

- Compare demographics like age, sex at birth, ethnicity, BMI between the NaCl-rich and the NaCl-poor arm. Means and standard deviation per group (or median, interquartile range as appropriate) will be reported. For ethnicity and sex, numbers and percentages are reported.
- Compare chronic comorbidities: HEFrEF, chronic kidney failure, chronic liver disease Child-Pugh B or C, diabetes mellitus type 1 and 2, hematologic or metastatic cancer between the NaCl-rich and the NaCl-poor arm (observed frequencies and percentages)
- Compare time from hospital admission to ICU admission (median, IQR)
- Compare time from ICU admission to randomization (median, IQR)
- Compare admission variables like source, type and main reason for admission between the NaCl-rich and the NaCl-poor arm. Sepsis or septic shock at admission will be reported per arm (observed frequencies and percentages).
- Compare severity score (SMS-ICU) and organ-failure score (SOFA) as well as individual markers of organ failure (vasopressor use during first ICU day, P/F ratio at admission (hypoxic respiratory failure

P/F ratio <150), use of invasive and non-invasive respiratory support during first ICU day, mechanical ventilation at randomization and renal replacement therapy during first ICU day) between the NaCl-rich and the NaCl-poor arm. For the categorical variables observed frequencies and percentages are reported, for the numeric variables mean (SD) or median (IQR) as appropriate.
- Compare chronic treatment with loop diuretics between the NaCl-rich and the NaCl-poor arm (observed frequencies and percentages).
- Compare baseline sodium and chloride levels between the NaCl-rich and the NaCl-poor arm (mean (SD) or median (IQR) as appropriate).
- A consort flow diagram will be produced to get an overview of the number of patients available at each stage: eligibility, randomisation, inclusion, discontinuation and follow-up.

1.11.3.2 Primary outcome analysis

The primary analysis will compare the primary outcome DAWOLS90 in the NaCl-rich and the NaCl-poor arm using a Mann Whitney test.

1.11.3.3 Secondary outcome analysis

- Different sensitivity analyses will be performed on the primary outcome. The Van Elteren test adjusted for the stratification variables site, mechanical ventilation at randomisation and surgical admission will be performed. A sensitivity analysis on the primary outcome in a regression model that has a good fit (different models can be considered linear regression, general linear model with Poisson distribution or negative binomial distribution) and where besides intervention (NaCl-rich or NaCl-poor) other variables like age, sex, trial site, mechanical ventilation at randomization, chronic kidney disease, sepsis/septic shock, hypoxic respiratory failure (P/F ratio <150), hematologic or metastatic cancer, surgical admission and severity of illness score (SMS-ICU) can be included. Beside considering solely the treatment arm as being either NaCl-rich or NaCl-poor, treatment volume will be added to the model as a continuous variable using actual proportion of cumulative NaCl-rich and NaCl-poor volumes administered and interaction between volume and treatment arm will be considered.

- For the binary secondary endpoints such as the occurrence of moderate and severe hyponatremia, moderate and severe hypernatremia, moderate and severe hyperchloremia, moderate hypoglycemia, new-onset AKI, new-onset RRT, new-onset need for mechanical ventilation, ICU and hospital mortality Fisher's exact test for unadjusted comparisons (or Chi-square test if assumptions allow) and a logistic regression model for adjusted comparisons will be considered. The numeric variables: days without renal replacement therapy at D90, ventilator-free days at D90, days alive and out of hospital at D90, proportion of ICU days during which IV loop diuretics were administered, proportion of hyperglemia over all glycemia measurements, cumulative fluid balance from ICU admission to start IV loop diuretic will be fitted with a linear regression model (or models comparable to primary outcome if assumptions are not met). In both models there will be corrected for other variables like age, sex, trial site, mechanical ventilation at randomization, chronic kidney disease, sepsis/septic shock, hypoxic respiratory failure (P/F ratio <150), hematologic or metastatic cancer, surgical admission and severity of illness score (SMS-ICU).

- For the time from randomization to first use of IV loop diuretics, a time-to-event analysis will be done comparing the NaCl-rich and NaCl-poor arm using a Kaplan-Meier plot and log rank test. A Cox proportional hazards model can be considered if confounders need to be added.

- Mean daily glycemia for each ICU day are compared between the two arms using a linear mixed model.

- The outcomes ICU and hospital length of stay will be modeled using a time-to-event analysis with death as a competing risk to compare the two arms.

- For ICU and hospital mortality a time-to-event analysis will be considered to compare the two arms.

- The efficacy and exploratory endpoints will be looked at graphically (taking into account diuretic use), described with descriptive statistics and if data allows modelled using linear mixed models (as they

are measured repeatedly). For the exploratory endpoints the linear mixed models will also allow to study associations among the different endpoints.

- The following subgroup analyses are performed:
  - Patients with the following chronic comorbidities
    - Chronic liver disease Child-Pugh B or C
    - HEFrEF (LVEF ≤40%)
    - Chronic kidney disease (eGFR <60 ml/kg/1.73m²)
  - Patients with the following conditions at admission
    - Sepsis/septic shock (sepsis 3.0 definitions)
    - AKI creatinine stage 2 or higher (KDIGO classification)
    - Hypoxic respiratory failure (P/F ratio <150)

- We will consider three analysis sets:
  - Modified intention-to-treat population: All randomized patients with a signed written informed consent (see Informed Consent Procedure). In the unlikely event that a patient, upon regaining full capacity, requests complete deletion of their data, those data will be excluded from this analysis set.
  - A per-protocol population are the patients from the modified intention-to-treat population without major protocol deviations.
  - SALADIN substudy analysis set: the patients from the modified intention-to-treat population entered in the substudy and fulfilling the SALADIN in- and exclusion criteria

The primary endpoint will be considered in the modified intention-to-treat and the per-protocol population. Primary conclusion for the primary endpoint will be based on the modified intention-to-treat population. The modified intention-to-treat population will also be used for the subgroup analysis on the primary endpoint. The safety and efficacy endpoints will be considered in the modified intention-to-treat and the per-protocol population. The exploratory endpoints will only be considered in the modified intention-to-treat population. The SALADIN endpoints will only be considered in the SALADIN substudy analysis set.

1.11.3.4 Procedure(s) to account for missing or spurious data

The study coordinator follows up on the missing data and records any reasons for missing data in patient file (medical record) and the eCRF (REDCap).

If less than 10% of data are missing for any primary or secondary outcome, a complete case analysis without imputation of missing values will be performed. If missing data are more than 10%, it will be assessed whether data are 'missing completely at random' (MCAR criterion) based on a rational assessment of the pattern of missing data and Little's test in case of doubt. If it is concluded that data are not MCAR, multiple imputation using chained equations will be performed by creating 20 input datasets under the assumption that the data are 'missing at random'.
In any multiple imputation, we will use all relevant outcomes and the stratification variables (site, mechanical ventilation at randomization, surgical admission), age, sex, chronic kidney disease, hematologic or metastatic cancer, sepsis/septic shock, hypoxic respiratory failure (P/F ratio < 150) and severity of illness score (SMS-ICU). Multiple imputation will be performed separately in the two intervention groups before pooling the full dataset, and will serve as a sensitivity analysis to the unadjusted, non-imputed analysis.

1.11.3.5 Other statistical considerations

Interim analysis

We will conduct one interim-analysis when 320 participants have been followed up for 90-days.
The interim analyses will be performed by the unblinded statistician. In the interim analysis, the primary outcome will be looked at with use of the conservative Haybittle-Peto boundary which will allow the final analysis to be performed using an unchanged level of significance of 0.05.

In case the DSMB recommends to stop the trial, the DSMB will discuss and recommend on whether the final decision to stop the trial will be made after the analysis of all participants included

at the time (including participants randomized after participant number 320) and whether a moratorium shall take place (setting the trial on hold) in the further inclusion of participants during these extra analyses. If further analyses of the participants included after 320 participants is recommended, the rules for finally recommending stopping of the trial should obey the Haybittle-Peto boundary. The DSMB will submit their recommendations to the TMG, which make the final decision regarding the continuing, pausing or stopping of the trial as described in the DSMB charter.
The trial will not be stopped for futility as an intervention effect less than a 16% relative risk reduction may be clinically relevant. However, the DSMB can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety.

1.12 DATA HANDLING

1.12.1 Data collection tools and source document identification

Data	ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies)."
Source Documents	ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study)."
Electronic Case Report forms	An electronic case report form ((e)CRF) system will be used by all participating sites to collect the individual patient data required by the study protocol. There is one primary source for the collection of study data. For data collected during routine clinical visits (clinical findings, observations, laboratory data, etc.), the participating site’s (electronic) medical record will be used as a primary source.The (e)CRF data will be used to perform the statistical analyses for the study, as described in Section 1.11.3.

The (e)CRF system will not be used as a primary source of data.

More details on data handling can be found in the Datamanagement Plan.

1.12.2 Archiving

Regarding the archiving period of data of experiments according to CTR 536/2014 and the Belgian law of May 7th 2017 regarding clinical studies with IMP: both digital files and paper files must be kept 25 years after completion of the study with IMP.
Patient (hospital) files will be archived for 30 years.

The institution/investigator shall archive the investigator site file ("ISF") at the institution using an electronic investigator site file binder solution specified by the Sponsor ("eISF Solution"). The ISF shall include all "Essential Documents", which are all documents as required by applicable laws, including in particular all documents relating to the study which allow evaluation and verification of the conduct of the study and the quality of the data generated. The institution and the investigator will be responsible for uploading and updating all Essential Documents in the ISF and the eISF Solution, in accordance with applicable laws. To the extent institution/investigator is required by applicable laws to upload and/or update Essential Documents and/or other data in the ISF/eISF Solution that would allow Sponsor to identify study subjects, institution/investigator may only do so in designated folders with proper protection, with Sponsor having no access to such folders. Institution/investigator may not upload any Essential Documents or other data into the ISF/eISF Solution in a manner that would allow Sponsor to identify study subjects.

1.13 MONITORING, AUDIT & INSPECTION

Before study initiation, at a site initiation visit a representative from the Sponsor will review the protocol and data capture requirements (i.e. (e)CRFs) with the local investigators and their staff. During the study, field monitors employed by the Sponsor (belonging to the CTC) will employ several methods of ensuring protocol and Good Clinical Practice compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture and data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrolment, and to ensure that study treatment is being dispensed and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by the centralized Sponsor research associate (CRA).

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital medical records) containing demographic and medical information, and the results of any other tests or assessments. All information on (e)CRFs must be traceable to these source documents in the patient's file. The investigators must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Sponsor's monitoring standards require verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. The latter and additional checks of the consistency of the source data with the (e)CRFs are performed according to a study-specific detailed monitoring plan. This monitoring plan will be approved by CI. The monitoring visits including site initiation visit and close out visit will be performed at each site. Any significant deviation from the planned monitoring timelines will be explained and documented in the monitoring report. If necessary, an amendment of the monitoring plan will be drawn up and approved again by CI.

If study sites do not register patients or stop enrolment, no regular monitoring visit will be planned. In the case of long-term absence (more than 4 months) of research activities, the central study team will ensure the research team is adequately trained when the research activity is restarted.

No information about the identity of the patients will be disclosed in the (e)CRF.

1.14 ETHICAL AND REGULATORY CONSIDERATIONS

1.14.1 Waiving of pregnancy testing for WOCBP

We define WOCBP as all women who are not postmenopausal or permanently sterile. We define postmenopausal state as ≥12 months of amenorrhea without an alternative medical explanation in women aged ≥50 years. Permanent sterility is defined as prior hysterectomy, bilateral oophorectomy, or bilateral salpingectomy. We do not to mandate pregnancy testing in WOCBP for the following reasons:

1/ The CRUSADERS trial is conducted in a low-risk, low-intervention context. All products involved in the study are widely used in critically ill pregnant women in ICUs worldwide on a daily basis, and do not carry reproductive risks that would necessitate additional precautions in this context. We screened the SmPC of each of the products used in the study arms and found the following:

- Plasma-Lyte A is described in its SmPC as safe during pregnancy, including for use during caesarean section.
- Glucose 5% and Glucose 3.3% in NaCl 0.3% carry in their SmPC only warnings related to use *during labour*, due to transient fetal hyperglycemia and neonatal rebound hypoglycemia. These effects are irrelevant in the ICU setting and further mitigated by the fact that hyperglycemia is very tightly controlled in all ICUs as standard of care.
- NaCl 0.9% includes in its SmPC a caution only for use *during labour* when combined with oxytocin.

While the CRUSADERS trial is formally categorized as an IMP study under EU Regulation 536/2014, this classification arises solely from the fact that the trial evaluates the effect of fluid composition on *clinical outcomes*, particularly mortality and organ support. As per the regulation, any use of medicinal products in a randomized trial intended to generate evidence on efficacy or safety classifies them as Investigational Medicinal Products, even when fully authorised and used in common clinical settings. However, in all other respects, CRUSADERS adheres to the principles of a non-IMP, low-intervention trial:

- All study fluids are commercially available, authorised products, including Plasma-Lyte, NaCl 0.9%, Glucose 5%, and Glucose 3.3% in NaCl 0.3%.
- These fluids are used routinely and daily in ICU practice worldwide, including in pregnant women.
- Their use in the trial does not deviate from local clinical practice in terms of dose, route, or therapeutic intent.
- The monitoring and diagnostic procedures used in the trial are entirely within standard ICU care and do not pose additional risk or burden.

2/ In routine ICU practice, many medications with far less data on pregnancy safety are used out of clinical necessity, as the maternal condition carries more risk than the treatment itself.

3/ Routine pregnancy testing in the ICU raises some additional and unwanted ethical concerns that we want to avoid. Many eligible patients are unconscious or unable to provide consent at the time of enrollment, and communication with next of kin is often needed. Performing pregnancy testing under these conditions—especially when it does not inform any change in management or risk—may violate patient privacy unnecessarily, with no added safety benefit.

1.14.2 Regulatory review & reports

- Before the start of the study, approval will be sought from the regulatory authorities for the study protocol, informed consent forms and other relevant documents e.g. advertisements and information letters
- Substantial amendments that require review by regulatory authorities will not be implemented until a favourable opinion for the study is granted
- All correspondence with the regulatory authorities will be retained in the (electronic) Trial Master File/(electronic) Investigator Site File
- It is the Chief Investigator's responsibility to produce the annual reports as required.

- The Sponsor will notify within 15 days each Member State concerned of the start of a clinical study in relation to that Member State through CTIS.
- The Sponsor will notify within 15 days each Member State concerned of the first visit of the first participant in relation to that Member State through CTIS
- The Chief Investigator will notify the regulatory authorities through the EMA database (CTIS) within 15 days of the end of the study in each MS concerned
- If the study is ended prematurely, the Chief Investigator will notify within 15 days the regulatory authorities through the EMA database (CTIS) , including the reasons for the premature termination
- The Sponsor will notify with 15 days each Member State concerned of a temporary halt of a clinical study in all Member States concerned for reasons not affecting the benefit-risk balance through CTIS
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, It shall be accompanied by a summary written in a manner that is understandable to laypersons to the regulatory authorities through the EMA database (CTIS)

1.14.3 Peer review

The final summary of this protocol is sent to all candidate participating centres for further review, commenting and discussion. A TSC (including local PIs) will be organised to have discussion and approval on in- and exclusion criteria as well as on the procedure. The current version of the full proposal is therefore based on the comments expressed by the candidate centres.

Peer review has been independent, expert, and proportionate:

- Expert: The above-mentioned reviewers have knowledge of the relevant discipline to consider the clinical and/or service-based aspects of the protocol and have the expertise to assess the methodological aspects of the study.
- Proportionate: Peer review is considered to be commensurate with the size and complexity of the study. This multicentre study requested a higher level of peer review (more reviewers with broader expertise and often independent review committee or board), and international peer review.

1.14.4 Public and Patient Involvement

A former ICU patient has been sought to be member of the Trial Steering Committee as an expert by experience.
This member gave input during a dedicated meeting on

- the design,
- the interventions,
- the informed consent procedure,
- different secondary endpoints
- the conduct of the Day 90 visit.

The minutes of this meeting are made available to the public.
She also agreed to review the patient materials (informed consent documents).

Also the PPI board of Antwerp University Hospital will review the patient materials for clarity. (informed consent documents).

1.14.5 Regulatory Compliance

The study conduct will comply with any and all applicable laws and local requirements, including but not limited to

- the International Conference on Harmonisation Guidelines (ICH Guidelines),
- the Belgian law of May 7th 2017 regarding clinical studies with IMP

In accordance with the aforesaid applicable laws, regulations and guidelines, the study will not commence until a Clinical Trial Authorisation (CTA) is obtained from regulatory.

1.14.6 Protocol compliance

The study will be carried out in full compliance with the final version of the protocol. Waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the study protocol.

All protocol deviations that occur during the protocol which are related to a patient will be documented in the patient file (medical record) and (e)CRF. The (e)CRF deviation log will capture the deviation description, deviation type, deviation date, date identified, relation to adverse event. If a protocol deviation is related to more than one patient this deviation must be recorded in the (e)CRF of each patient. General protocol deviations will be recorded on a protocol deviation log and will be present in (e)ISF and (e)TMF. The sponsor will have to score all the deviations (major and minor). In case the deviation is scored major a corrective action should be started.

1.14.7 Notification of Serious Breaches to regulation and/or the protocol

A serious breach is defined as a breach which is likely to effect to a significant degree:

i. the safety or physical or mental integrity of the subjects of the study; or
ii. the scientific value of the study.

1.14.8 Data protection and patient confidentiality

Confidentiality will be maintained and as will the manner of how the study is compliant with the requirements of the Belgian and European Privacy legislation (https://www.dataprotectionauthority.be/legislation-and-standards). All investigators and study site staff must comply with the requirements of the above legislation on the protection of privacy in relation to the processing of personal data, with regards to collection, storage, processing, and disclosure of personal information.

Personal information collected at the study site will be maintained and kept secure by the PI. Data entered into the study software will be coded and depersonalised.

The data and linking code will be kept in separate locations using encrypted and password protected digital files. Access to these data will be limited to only those who need it for the purposes of quality control, audit, and analysis.

1.14.9 Access to the final study dataset by other parties

Chief Investigators and study statisticians appointed by the Chief Investigators have access to the full dataset. Other individuals can be granted access upon advice from the TSC. Data transfers are the subject of individual data share agreements. Also site investigators can receive access to the full dataset if a formal request describing their plans is approved by the steering committee.

REFERENCES

See end of document.

APPENDICES

APPENDIX 1. RISK ASSESSMENT OF THE STUDY INTERVENTION(S)

Risks associated with study interventions
☒ A ≡ Comparable to the risk of standard medical care
☐ B ≡ Somewhat higher than the risk of standard medical care
☐ C ≡ Markedly higher than the risk of standard medical care

Justification: All the used study fluids are authorised medicinal products for every indication used in the study, either for maintenance fluid therapy, for line patency and for dissolving medications. As such, two different standards-of-care are compared and nothing is prescribed during the study that is not being prescribed in current practice in different hospitals all over the world. This classifies the study as a low-intervention trial.

What are the key risks related to therapeutic interventions you plan to monitor in this study?		How will these risks be minimized?		
IMP	Body system/Hazard	Activity	Frequency	Comments
NaCl-poor arm	Hyponatremia	Routine daily lab assessment in the ICU (central lab and POCT)	At least daily, often 4+ times daily	Standard of care
NaCl-poor arm	Hyperglycemia	Routine daily lab assessment in the ICU (POCT)	At least daily, often 4+ times daily	Standard of care
NaCl-rich arm	Hypernatremia, hyperchloremia	Routine daily lab assessment in the ICU (central lab and POCT)	At least daily, often 4-6 times daily	Standard of care
NaCl-rich arm	Fluid accumulation	Daily clinical assessment	Depending on clinical picture	Standard of care

The SAR's above are common in the ICU and often not related to study treatment, so exempt from reporting. A Data and Safety Monitoring Committee will be put in place and review predefined more critical SAR's 4 times throughout the course of the study.

Outline any processes (e.g. IMP labelling +/- accountability +/- study specific temperature monitoring) that have been simplified based on the risk adapted approach.
Based on the risk-adapted approach in the CRUSADERS trial, several processes have been simplified to ensure efficient trial conduct while maintaining regulatory compliance:

- Lower labeling requirements: Since the study is a low-intervention trial, no additional labeling is required for dissolving medications, as all medications compatible with both study treatments can be dissolved interchangeably. Maintenance fluids are labeled with the study name, intervention arm and usual patient identifier to ensure proper administration.
- Standard monitoring of IMP: Study fluids are stored under routine hospital storage conditions, following the manufacturer's specifications. Temperature monitoring adheres to standard hospital pharmacy protocols, without additional study-specific requirements.

- Simplified SAE reporting: Serious Adverse Reactions (SARs) are recorded only if predefined as study-relevant or if classified as Suspected Unexpected Serious Adverse Reactions (SUSARs). Other SAEs follow routine medical documentation without mandatory reporting in the eCRF.

APPENDIX 2. SAFETY REPORTING FLOW CHART (IF NOT DESCRIBED ABOVE)

	Findings	Reporting	Timing	Party
SAE	Any SAE	No	N/A	N/A
Adverse reactions (recorded in medical records)	• Local irritation, local pain, extravasation, pruritus, phlebitis and thrombophlebitis (all study fluids). • Urticaria (all study fluids) • Chills or pyrexia (PlasmaLyte) • Metabolic acidosis (NaCl 0.9%) and alkalosis (PlasmaLyte) • Hypokalemia (glucose 5%) and hyperkalemia (NaCl 0.9%) • Mild dysnatremia and dyschloremias • Cardiac arythmias (PlasmaLyte) • Paralytic ileus (PlasmaLyte) • Diarrhea (PlasmaLyte)	No	N/A	N/A
Adverse reactions (recorded in medical records and eCRF)	• Hyperglycemia (attributable hyperglycemia outside classic stress hyperglycemia in the ICU is rare) (Glucose 5%) • Electrolyte disorders, such as hyponatremia (glucose 5%), hypernatremia (NaCl 0.9% and PlasmaLyte) and hyperchloremia (NaCl 0.9%) • Symptomatic or asymptomatic fluid and sodium retention, recorded in the form of diuretic use and daily and cumulative fluid balance	No	N/A	N/A
Serious adverse reactions	• New onset (>48h) symptomatic severe hypoNa (<125) • Central pontine myelinolysis (CT, MRI) after new onset hypoNa • New onset (>48h) symptomatic severe hyperNa (>155) (seizures) • New onset (>24h) severe hypoglycemia (<40 mg/dL) • New onset (>48h) clinical refeeding Σ • New onset (>48h) Wernicke encephalopathy • New onset (>48h) starvation ketosis • Anaphylactic reactions	Yes	< 72h	Sponsor
SUSAR	Any SUSAR	Yes	<24h	Sponsor EMA (by Sponsor) DSMB (per 6 months)

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