Effects of goal-directed fluid management guided by a non-invasive device on the incidence of postoperative complications in neurosurgery: a multicenter, prospective, randomized, controlled study

CLINICAL TRIAL PROTOCOL

Short title:	Effects of GDHT using a non-invasive hemodynamic monitoring in elective neurosurgery
Protocol code:	NCHGDT
EU CTR:	2024-511153-21-00
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Sponsor:	Fakultní nemocnice Brno Jihlavská 20 625 00 Brno, Czech Republic

STATEMENT

The following persons undertake to conduct the study “Effects of goal-directed fluid management guided by a non-invasive device on the incidence of postoperative complications in neurosurgery: a multicenter, prospective, randomized, controlled study” according to this protocol and in compliance with applicable national and international requirements, mainly:

- Regulation EU No. 536/2014
- Act No. 378/2007 Coll., on Pharmaceuticals, as amended;
- Decree No. 463/2021 Coll., on Detailed conditions governing the conduct of clinical trials on medicinal products, as amended;
- Good Clinical Practice – ICH E6(R2);
- Declaration of Helsinki, as amended.

		Signature	**Date**
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CONTENTS

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
APCO	Arterial Pressure Continuous Output
aPTT	activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
ASA	American Society of Anesthesiologists
CI[a]	Cardiac Index
CI	Confidence Interval
CO	Cardiac Output
CP	Cardiac Power
CPAP	Continuous Positive Airway Pressure
CPI	Cardiac Power Index
CT	Computerized Tomography
CTIS	Clinical Trial Information System
CVP	Central Venous Pressure
DBP	Diastolic Blood Pressure
DCI	Delayed Cerebral Ischemia
DO2I	Delivery Oxygen Index
DVT	Deep Vein Thrombosis
ECG	Electrocardiography
eCRF	electronic Case Report Form
eGRF	estimated Glomerular Filtration Rate
EVCTM	EudraVigilance Clinical Trial Module
e.g.	exempli gratia
GCP	Good Clinical Practise
GDHT	Goal Directed Hemodynamic Therapy
GOS	Glasgow Outcome Scale
HR	Heart Rate
ICF	Informed Consent Form
ICH E6	harmonized guideline for good clinical practise
ICU	Intensive Care Unit
ICU LOS	Intensive Care Unit Length of Stay
i.e.	id est
IMP	Investigational Medicinal Product
i.v.	intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LOS	hospital length of stay
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NMBA	neuromuscular blocking agent
OR	odds ratio
PE	Pulmonary Embolism
PEEP	Positive End-Expiratory Pressure
RBC	red blood cells
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
SpO2	Saturation of Peripheral Oxygen
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Stroke Volume
SVI	Stroke Volume Index
SVV	Stroke Volume Variation
TCI	Target Controlled Infusion
TFC	Thoracic Fluid Content
TIVA	Total Intravenous Anaesthesia
TPR	Total Peripheral Resistance
TPRI	Total Peripheral Resistance Index
UADR	Unexpected Adverse Drug Reaction
VET	Ventricular Ejection Time

1. CLINICAL TRIAL BACKGROUND

1.1. Goal-directed hemodynamic therapy (GDHT)

Goal-directed hemodynamic therapy (GDHT) is a complex group of interventions aimed at improving oxygen delivery and tissue perfusion, successfully used in several surgical indications during perioperative period. Many devices - from invasive to minimally invasive - can be used to determinate various hemodynamic values, which can be targeted to predefined goals through titration of intravenous fluid and vasoactive drugs [1]. GDHT has been shown to reduce postoperative complications (e.g. acute kidney disease, pulmonary oedema, wound infection) and decrease hospital length of stay in patients undergoing major abdominal, urological, gynecological and orthopedic procedures [2,3].

Due to the wide application of this methodology in surgery, several meta-analyses processing data from clinical trials have been published in the last decade. Jessen et al. [4] identified 76 comparative studies in which GDHT protocols including fluid therapy to optimize stroke volume (or related parameter) were compared with standard care. Analysis of data from 9081 patients undergoing non-cardiac surgery showed a moderate-certainty-of-evidence reduction in postoperative pneumonia, surgical site infection and anastomotic leakage in the GDHT arms, while effects on mortality and hospital length of stay were not demonstrated.

A systematic review to assess the effect of GDHT exclusively on post-operative pulmonary complications in patients undergoing surgery performed Dushianthan et al. [5]. A significant reduction in total pulmonary complications (OR 0.74, 95% CI 0.59 to 0.92) in GDHT group was demonstrated in a sample of 9548 participants (66 studies in total). Meta-analysis suggests that the use of GDHT using fluids with inotropes and/or vasopressors, but not fluids alone, reduces the development of post-operative pulmonary infections and pulmonary oedema in patients undergoing abdominal and cardiothoracic surgery. The pitfalls of meta-analyses focusing on GDHT in general, such as the clinical heterogeneity of patients, interventions and outcomes, are pointed out in the review by Kaufmann et al. [6]. Saugel et al. [7] recommend consistently including only trials using similar perioperative hemodynamic treatment strategies (hemodynamic target variables, target values, and triggered interventions) in meta-analyses to avoid oversimplification that could lead to incorrect conclusions.

1.2. GDHT in neurosurgical interventions

Patients undergoing major neurosurgery are at risk for inadequate intravascular volumes. Fluid overload can contribute to worsening brain oedema. On the other hand, the administration of diuretics to reduce brain oedema, reduction of preoperative fluid intake, and intraoperative blood loss leads to a decrease in intravascular volume and thus to a decrease in blood flow and oxygen supply to the brain and other tissues, resulting in organ dysfunction. The use of goal-directed hemodynamic therapy (GDHT) guided by non-invasive measurement of hemodynamic parameters aims to optimize the intravascular volume, thereby improve blood flow through tissues and reduction of the incidence of postoperative adverse events.

1.2.1. Spine surgery

In contrast to the surgical fields mentioned above, only limited data are currently available on the GDHT efficacy in neurosurgery. For spine surgery in the prone position, conflicting results from several monocentric studies are available. Picard et al. [8] confirmed that intraoperative use of esophageal Doppler and optimalization of perioperative fluid management is feasible and may help to reduce the duration of hypotensive episodes during spinal surgical procedures. Conversely, a study by Wongtangman et al. [9], despite similar clinical characteristics, did not demonstrate significant benefits of the GDHT protocol with respect to intraoperative hypotension, blood transfusion, or postoperative complications in patients undergoing complex spine surgery. Results published by Abdelhamid et al. also failed to demonstrate a benefit of the GDHT compared to conventional fluid management in 66 adult patients undergoing spine surgery. The goal-directed fluid management therapy dependent on plethysmographic variability index did not reduce the intraoperative total crystalloid administration or requirements for blood transfusion [10].

Maintanance of targed levels of mean arterial pressure (MAP) and stroke volume (SV) through fluid therapy and vasopressor administration with minimally invasive hemodynamic monitoring was used by Andrzejewska et al. in a prospective pediatric case-control study in elective scoliosis surgery [11]. The GDHT group (n=24, mean age 14 years) showed a significantly shorter duration of hypotension (mean arterial pressure < 60 mmHg), reduced hospital stays, smaller decreases in postoperative hemoglobin levels and shorter times from the end of surgery to extubation.

1.2.2. Brain surgery

A study investigating the effects of a GDHT strategy in patients undergoing high-risk brain surgery (GDHT group [n=73] vs. control group [n=72]) where appropriate fluid management is necessary due to impending brain oedema was conducted by Luo et al. [12]. According to published results, ICU length of stay was shorter (3 days [1–5] vs. 6 days [3–11], p = 0.001) and ICU costs were lower in the GDHT group. The total number of complications (46 vs. 99, p = 0.043) and the proportion of patients who developed one or more complications (19.2 vs. 34.7%, p = 0.034) were less in the GDHT group compared to patients who received standard care.

The ability of the GDHT approach compared with standard clinical care to reduce the rate of delayed cerebral ischemia (DCI) after subarachnoid hemorrhage was investigated by Anetsberger et al. [13] in a prospective randomized controlled trial with 108 adult subjects. The primary outcome (DCI) occurred in 13% of patients in the GDHT group (n=54) and in 32% of patients in the control group (n=54). Moreover, reduced rate of DCI was associated with a better functional outcome (GOS=5) 3 months after discharge.

Another study [14] was designed to assess the influences of arterial pressure continuous output (APCO) derived SVV-guided fluid management on postoperative complications and outcome in patients undergoing supratentorial neoplasms surgery. Based on data obtained from 66 patients, SVV-guided fluid management was associated with a lower incidence of postoperative complications and did not induce additional risk of brain oedema (degree of brain oedema 1 day postoperatively did not differ between study groups [3 vs. 3, P=0.96]).

Finally, a study conducted in 48 patients scheduled for elective craniotomy was designed to test whether intraoperative goal-directed fluid management using SVV-guided 0.9% normal saline administration could alleviate metabolic acidosis compared with CVP-based fluid administration. Contrary to the hypothesis, intraoperative targeted fluid therapy based on SVV values from the FloTrac/Vigileo™ system did not reduce the severity of metabolic acidosis in patients undergoing brain tumor resection compared with CVP-guided fluid therapy [15].

1.3. The Starling™ SV System

The Starling™ SV System is a portable, non-invasive cardiac output (CO) monitoring device based on BIOREACTANCE® technology that is capable of predicting response to intravenous fluids in critical care situations similar to invasive methods (e.g. esophageal Doppler). It also measures heart rate (HR), stroke volume (SV), stroke volume variation (SVV), ventricular ejection time (VET), mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), saturation of peripheral oxygen (SpO2) and thoracic fluid content (TFC). In addition, the system calculates some other clinical parameters such as cardiac index (CI[a]), stroke volume index (SVI), total peripheral resistance (TPR), total peripheral resistance index (TPRI), cardiac power (CP), cardiac power index (CPI) or oxygen delivery index (DO2I). The Starling™ SV System is registered in the Registry of Medicinal Devices under reference number 00538564 and is not subject to the obligation of any clinical tests of the medical device in this clinical trial. Only limited data have been published on its use in neurosurgery [16], the expansion of this knowledge is one of the goals of this clinical trial.

1.4. Study rationale

Surgical procedures, particularly in neurosurgery, pose significant challenges in fluid management. The balance between maintaining adequate intravascular volume to ensure sufficient organ perfusion while avoiding fluid overload is crucial for optimizing patient outcomes. Neurosurgical patients face unique factors contributing to fluid imbalance, including preoperative diuretic use, decreased oral intake, and the risk of intraoperative blood loss. These factors can lead to hypovolemia, compromising organ perfusion and increasing the risk of complications. Conversely, excessive fluid administration can exacerbate issues like cerebral edema and compromise cardiac function.

The goal-directed hemodynamic therapy (GDHT) approach has shown promise in various surgical subspecialties, demonstrating reductions in perioperative complications, shorter hospital stays, and decreased costs. However, its application in neurosurgery remains understudied. The primary aim of this study is to determine whether optimizing fluid management during elective neurosurgical procedures reduces the occurrence of postoperative adverse events in adult patients compared to standard care.

1.5. Anticipated risks and benefits

The feasibility and safety of a GDHT approach using the non-invasive Starling™ SV System in neurosurgery was evaluated in a pilot study (34 adult subjects). No patient had unsatisfactory relaxation of brain tissue after surgery or brain oedema requiring therapy during surgery or 24 hours after surgery. Major complications occurred in two (11.8 %) patients in the

GDHT group and six (35.3%) patients in the control group (p = 0.105) [17]. The Starling™ SV System is an approved medical device, which will be used in accordance with its stated purpose and manufacturer's recommendations. As part of this clinical trial, only registered medicinal products that are standardly used in the given indication will be used, so there is no assumption of the emergence of new safety signals resulting from the use of these products.

The clinical outcome of an individual participant in this trial may or may not be improved. If effective, GDHT might help to optimize intravascular volume, prevent fluid overload or hypovolemia and thereby reduce the incidence of postoperative adverse events in adult patients undergoing elective neurosurgery. As elective neurosurgical procedures are generally high-risk, all participants in this clinical trial will be provided with proper peri- and post-operative care and immediate medical attention will be provided in case of any unexpected events.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Aim of the study

This study aims to assess the safety and efficacy of GDHT using the non-invasive Starling™ SV System in elective neurosurgery. The tested group of patients (n=70) will be compared with a control group (n=70), where hemodynamic management will be guided by standard vital signs monitoring.

2.2. Primary objective(s) and endpoint(s)

The **primary objective** of the clinical trial is to determine the effect of GDHT guided by the non-invasive Starling™ SV System on the incidence of postoperative complications in patients undergoing neurosurgical intervention.

The following **primary endpoints** will be monitored to evaluate the primary objective:

1.) Incidence of adverse events and reactions according to following Adverse Events of Special Interest (AESI) in both study groups.

Monitored parameters (AESI): (YES/NO)

Detailed **definitions and grading of** individual **AESI** can be found in **Appendix A 14.1**

- Acute Kidney Injury (stage 2, 3 according to KDIGO guidelines)
- Acute Respiratory Distress Syndrome (ARDS, according to Berlin definition of Respiratory Distress Syndrome)
- Arrhytmia (moderate/severe)
- Cardiac arrest
- Cardiogenic pulmonary oedema (moderate/severe)
- Deep vein thrombosis (DVT; moderate/severe)
- Pulmonary embolism (PE)
- Gastrointestinal bleed (moderate/severe)
- Infection, source uncertain (moderate/severe)
- Laboratory confirmed bloodstream infection (moderate/severe)
- Myocardial infarction (moderate/severe)
- Pneumonia (moderate/severe)
- Paralytic ileus (moderate/severe)
- Postoperative haemorrhage (moderate/severe)
- Stroke (moderate/severe)
- Brain oedema (CT or MRI proven; moderate/severe)
- Surgical site infection (superficial; moderate/severe)
- Surgical site infection (deep; moderate/severe)
- Surgical site infection (organ/space; moderate/severe)
- Urinary tract infection (moderate/severe)

2.3. Secondary objective(s) and endpoint(s)

The **secondary objective** is to investigate the efficacy and additional safety parameters of GDHT guided by non-invasive advanced hemodynamic monitoring versus hemodynamic management guided by standard vital signs monitoring.

Secondary endpoints are as follows:

1.) Additional safety information

Monitored parameters:

- Duration of surgery (min)
- LOS (day of admission – day of discharge will be counted as 1 day)
- ICU LOS (day of admission – day of discharge will be counted as 1 day)
- 28-day mortality (number of patients who are not alive 28 days after randomization)
- Descriptive analysis of the incidence of any adverse events and reactions

2.) Comparison of hemodynamic characteristics and their changes over time between study groups

Monitored parameters:

- MAP (mmHg; before, after surgery)
- HR (Bpm; before, after surgery)
- SVV (%; before, after surgery)
- Number of episodes of hypotension[1]
- Number of vasopressor administrations

3.) Comparison of laboratory values of selected blood parameters and their changes over time between study groups

Monitored parameters:

- Hemoglobin (g/l; before, after surgery and 24 hours after surgery)
- Plasma lactate level (mmol/L; before, after surgery and 24 hours after surgery)

4.) Comparison of fluid balance and fluid therapy between study groups

Monitored parameters:

- Volume of blood loss (ml/kg; during surgery[2] and in the 24-hour postoperative period)
- Urinary output (ml/kg/hod; during surgery[2] and in the 24-hour postoperative period)
- Number of administered units of packed RBC (during surgery[2] and in the 24-hour postoperative period)

[1] MAP bellow 65 torrs [18]

[2] **duration of surgery** is considered as the time from the skin incision to the suture of the dura

- Number of subjects receiving transfusion (during surgery[2] and in the 24-hour postoperative period)
- Crystalloid and colloid solutions consumption (type and total volume of infusion during surgery[2] and in the 24-hour postoperative period)
- Boluses of crystalloids (ml; during surgery[2])

3. TRIAL DESIGN

The **NCHGDT** is a multicenter, prospective, randomized, controlled trial comparing the efficacy and safety of two approaches to fluid management in elective neurosurgery; GDHT guided by the non-invasive Starling™ SV System versus hemodynamic management guided by standard vital signs monitoring. The study will be conducted at the University Hospital Brno, Czech Republic and in other Czech centers that have appropriate equipment for advanced hemodynamic monitoring. Optimal standard treatment will be achieved in both arms of the study using the current best treatment protocol. The anticipated sample size is 140 patients randomized into study groups in a 1:1 allocation ratio and followed up for 28 days after surgery. End of study is defined as the time of completion of the 28-day follow-up in the last patient. The expected duration of this clinical trial is 3 years.

4. TRIAL POPULATION

4.1. Inclusion criteria

Subjects will **be eligible** for the trial **if** they **meet all** of the following **criteria**:

1. Age ≥ 18 years
2. Elective brain surgery with an expected duration ≥ 2 h
3. Category 1-3 according to the ASA Physical Status Classification
4. Lateral or supine operative position
5. Signed the relevant informed consent form (more in Chapter 10.1)

4.2. Exclusion criteria

Subjects will **not be eligible** for the trial **if** they **meet any** of the following **criteria**:

1. Category 4 according to the ASA Physical Status Classification
2. Surgery for traumatic brain injury or acute hemorrhagic stroke
3. Awake brain surgery
4. Osmotherapy before surgery (with the exception of prophylactic administration of osmotic agents according to institutional standards)
5. Unavailability of hemodynamic monitoring data
6. Cardiac arrhythmia with irregular cardiac rhythm
7. Known hypersensitivity to the active substance or to any of the excipients of IMP (see Chapter 5)
8. Pregnancy and lactation

4.3. Randomization

Participants will be randomized in a 1:1 ratio to the two study arms (GDHT or STANDARD) using the eCRF REDCap database shortly before surgery by a member of the study team.

4.4. Blinding

The neurosurgeon, ICU staff and members of the study team collecting data will be blinded. The hemodynamic monitor will be placed in the operating room during all study interventions so that the neurosurgeon cannot see whether it is being used or not. Other study staff and attending physicians and other staff will not be blinded, as blinding is not possible when conducting the study intervention. The data management group and statisticians will work with a pseudo-anonymized data set.

4.5. Enrolment stopping rules

Enrolment of new subjects into the trial may be stopped in situations that could lead to an immediate risk to patients (e.g. epidemics of serious infectious diseases, etc.) or if a new toxicity of the study medication is newly identified.

4.6. Premature termination of participation in the trial

Reasons for early termination of a patient's participation include:

- Withdrawal of informed consent (subject's decision to withdraw for any reason);
- Important deviation in the process of informed consent (Chapter 10);
- Life-threatening adverse reaction related with IMP or study intervention at the discretion of the investigator;
- Pulmonary oedema or cardiac decompensation is suspected;
- Newly-emerged pregnancy of a participant after the enrolment;

Subjects **can terminate their participation prematurely** at any time at their request for any reason, but they must notify the investigator. The investigator must contact the sponsor to report the premature discontinuation.

The investigator must:

- Instruct the participant about the right on early termination of participation;
- Assure him/her that the end of participation will not affect the attitude of the physician, or further treatment and its quality;
- Ask for discussing this decision with the investigator in advance;
- Make a note in the patient's medical records and eCRF about the date of early termination of participation.

The **sponsor** reserves the **right to discontinue the study** at any time if there is a significant safety concern, or insufficient recruitment despite intensified efforts to enrol patients, or if repeated poor study documentation occurs at a site. The trial can be discontinued by the decision of the **regulatory authority** or **ethics committee**, as well.

5. STUDY TREATMENT

5.1. ISOLYTE INF SOL

ISOLYTE INF SOL was chosen as a model preparation of crystalloid solution for intravenous administration in this clinical trial (ATC code: B05BB01). Detailed information on its pharmacodynamics, pharmacokinetics, excipients and other characteristics can be found in the SmPC.

Quantitative composition:

	500 ml	1000 ml
Sodium Acetate Trihydrate	2.32 g	4.63 g
Sodium Chloride	3.01 g	6.02 g
Potassium Chloride	0.15 g	0.30 g
Magnesium Chloride Hexahydrate	0.15 g	0.30 g

Electrolytes: Na^+ 137.0 mmol/l, K^+ 4.0 mmol/l, Mg^{2+} 1.5 mmol/l, Cl^- 110.0 mmol/l, CH_3COO^- 34.0 mmol/l

5.1.1. Pharmaceutical form and route of administration

Solution for infusion; intravenous administration

5.1.2. Marketing-authorization holder

Fresenius Kabi s.r.o., Na Strži 1702/65, Nusle, 140 00 Praha 4, Česká republika

5.1.3. Storage

Shelf life in intact packaging (before opening): Freeflex - 3 years, KabiPac - 3 years. Protect from cold or frost.

5.1.4. Dosing schedule

Dosage will be chosen and adjusted according to the investigator's decision in accordance with SmPC. A detailed description of the recommended dosage is included in the Chapter 6.3.

5.1.5. Contraindication

Administration of IMP is contraindicated in cases of:

- fluid overload (hyperhydration; especially with pulmonary oedema and congestive heart failure),
- severe renal dysfunction,
- metabolic alkalosis and
- hyperkalemia.

5.1.6. Adverse effects

The following adverse effects have been reported during administration of electrolyte solutions:

1. Disorders of metabolism and nutrition
   - hyperhydration and heart failure in patients with heart failure or pulmonary oedema (very common >1/10)
   - oedema due to excess water/sodium in the body (frequency not known)
2. General disorders and reaction at the site of application
   - febrile response, injection site infection, local pain or reaction, vein irritation, venous thrombosis or phlebitis extending from the injection site, and extravasation

At high doses, the dilution effect can often lead to dilution of individual blood components, e.g. coagulation factors and other plasma proteins, and to a decrease in hematocrit. In case of adverse effects, the infusion must be interrupted.

5.2. GELASPAN 4% INF SOL

GELASPAN 4% INF SOL was chosen as a model preparation of colloid solution for intravenous administration in this clinical trial (ATC code: B05AA06). Detailed information on its pharmacodynamics, pharmacokinetics, adverse effects, excipients and other characteristics can be found in the SmPC.

Quantitative composition:

	1000 ml
Gelatin Succinate	40.0 g
Sodium Chloride	5.55 g
Sodium Acetate Trihydrate	3.27 g
Potassium Chloride	0.30 g
Calcium Chloride Dihydrate	0.15 g
Magnesium Chloride Hexahydrate	0.20 g

Electrolytes: Na^+ 151.0 mmol/l, K^+ 4.0 mmol/l, Mg^{2+} 1.0 mmol/l, Ca^{2+} 1.0 mmol/l, Cl^- 103.0 mmol/l, CH_3COO^- 24.0 mmol/l

5.2.1. Pharmaceutical form and route of administration

Solution for infusion; intravenous administration

5.2.2. Marketing-authorization holder

B. Braun Melsungen AG, Carl-Braun-Str. 1, 34212 Melsungen, Germany

5.2.3. Storage

Shelf life in intact packaging (before opening): polyethylene bottles - 2 years, plastic bags (PVC-free) - 2 years. Store at a temperature of up to 25 °C. Protect from frost.

5.2.4. Dosing schedule

Dosage will be chosen and adjusted according to the investigator's decision in accordance with SmPC. A detailed description of the recommended dosage is included in the Chapter 6.3.

5.2.5. Contraindication

- hypersensitivity to solutions containing gelatin or to any of the excipients
- hypersensitivity to galactose-α-1,3-galactose (alpha-gal) or known allergy to red meat (mammal meat) and offal
- hypervolemia
- hyperhydration
- acute congestive heart failure

5.2.6. Adverse effects

The following adverse effects have been reported during administration of Gelaspan 4%:

- Very common (≥ 1/10): decreased hematocrit and decreased concentration of plasma proteins
- Common (≥ 1/100 to <1/10): relatively large doses of Gelaspan 4% cause dilution of coagulation factors and can therefore affect blood coagulation. After administration of large doses of Gelaspan 4%, the value of prothrombin time may increase and the activated partial thromboplastin time (aPTT) may be prolonged.
- Rare (≥ 1/10,000 to <1/1,000): anaphylactic/anaphylactoid reactions up to shock
- Very rare (< 1/10,000): tachycardia, hypotension, fever, chills
- Not known: nausea, vomiting, abdominal pain, decreased oxygen saturation

In the event of an anaphylactoid reaction, the infusion must be stopped immediately and the usual acute treatment instituted.

5.3. Prohibited medication

No prohibited medication is defined for the purposes of this clinical trial.

5.4. Concomitant medication

Fluids, vasopressors and inotropes listed in Chapter 6.3 (see detailed information on dosage) can be used to treat hypovolemia, hypotension and low cardiac output respectively.

6. COURSE OF THE TRIAL

6.1. Screening of eligible patients

Adult patients scheduled for elective neurosurgery will be screened for eligibility criteria after admission to the hospital. Study team members will perform the screening, and the principal investigator will regularly audit the accuracy of screening. Patients will be included if they meet all inclusion criteria and none of the exclusion criteria. After obtaining informed consent, each patient will be randomised to one of the trial arms. For details on obtaining the informed consent see Chapter 10.1

6.2. Clinical examinations and assessments

During the trial course, subjects will be monitored during hospitalization and after discharge. A summary of scheduled procedures is outlined in Chapter 6.3. For a graphic summary see Table 1.

Table 1: Clinical trial schedule

	STUDY PERIOD						
	Screening	**Allocation**	**Post-allocation**		**Hospital discharge**	**Follow-up**	**Premature termination**
TIMEPOINT	D_{-3-0}		D_1	D_2	D_{3-28}	D_{28}	*Anytime*
ENROLMENT:							
Eligibility criteria	**X**						
Informed consent	**X**						
Pregnancy testing[1]	**X**						
Randomization		**X**					
ASSESSMENTS:							
Demographic data[2]		**X**					
Fluid therapy[3]			**X**	**X**			
Laboratory testing[4]			**X**	**X**			
Hemodynamics[5]			**X**	**X***			
Adverse events			**X**	**X**	**X**	**X**	**X**
Postoperative complications (AESI[6])			**X**	**X**	**X**	**X**	**X**
Blood loss[7]			**X**	**X**			
Urinary output[8]			**X**	**X**			
Transfusion products consumption[9]			**X**	**X**			
Duration of surgery (min)			**X**				
ICU LOS (days)					**X**		
LOS (days)					**X**		
28-day mortality						**X**	
Reason for premature termination							**X**

1 urine pregnancy testing
2 age, sex, weight
3 type and volume (ml) during surgery and in the 24-hour postoperative period (for more details see Chapter 2.3, point 4.)
4 hemoglobin, plasma lactate level (for more details see Chapter 2.3, point 3.)
5 MAP, HR, SVV, number of hypotension episodes, number of vasopressor administrations (for more details see Chapter 2.3, point 2.)
6 for more details see Chapter 2.2
7 volume (ml/kg) during surgery and in the 24-hour postoperative period
8 volume (ml/kg/hod) during surgery and in the 24-hour postoperative period
9 number of administered units of packed RBC during surgery and in the 24-hour postoperative period
*except SVV

6.3. Study procedures

Day -3 to 0

- Eligibility screen – inclusion and exclusion criteria
- Informed consent procedure (Chapter 10.1)
- Pregnancy testing (see Chapter 7.8)
- Demographic data
- Randomization (more in Chapter 4.3)

Day 1

- Assessment of hemoglobin and plasma lactate level
- Recording blood loss and urinary output during and after surgery
- Transfusion products consumption
- Crystalloid and colloid solution consumption
- Monitoring of hemodynamic parameters
- Monitoring of adverse events and reactions including postoperative complications of special interest

Prior to surgery, study participants will receive regular premedication according to hospital standards.

General anaesthesia will be induced by intravenous administration of propofol. For attenuation of the hemodynamic response to laryngoscopy, opioid will be added. To facilitate intubation, a neuromuscular blocking agent (NMBA) will be used. After tracheal intubation, mechanical ventilation will be commenced with the following settings: tidal volume of 8–10 ml/kg and respiratory rate to maintain an end-tidal CO2 of 30–35 mmHg. Anaesthesia will be maintained with propofol infusion using TCI (target controlled infusion) or TIVA (total intravenous anaesthesia) and additional doses of opioids and relaxants will be administered at the discretion of the attending anaesthesiologist. The patients' temperature will be maintained at 36–37 °C.

Both groups will receive standard monitoring of vital signs through continuous electrocardiography, pulse oximetry, end-tidal CO2 measurement, and invasive monitoring of arterial blood pressure.

In the STANDARD arm, perioperative hemodynamic management and postoperative care will be at the discretion of the attending anaesthesiologist and intensivist, respectively. Hypotension with MAP < 65 mmHg will be managed with administration of a 250-ml bolus of balanced crystalloid over 10 min or 250-ml bolus of colloid over 5 min. The choice of fluid and number of boluses will be at the discretion of attending anaesthesiologist. If fluids are considered ineffective, a vasopressor will be added.

In the GDHT arm, non-invasive hemodynamic monitoring will be used (Starling™ SV hemodynamic monitor, Cheetah Medical Inc., 600SE Maritime Ave Suite 220, Vancouver, WA, USA) in addition to the monitoring used in the STANDARD arm. The Starling SV monitor uses

patented Bioreactance® technology and requires placement of only four sensors, which are skin electrodes similar to those used for ECG monitoring.

The extended monitoring will begin after the induction of general anaesthesia and resolution of any hypotension caused by the induction of general anaesthesia. This hypotension will be resolved with fluid bolus and vasopressor administration if necessary. Subsequently, a basal infusion will be initiated with balanced crystalloid solution at 3 $ml.kg^{-1}.h^{-1}$ with an infusion pump. We will then determine the optimal CI^a, defined by a value of at least 2,5 $l.min.m^{-2}$, a stroke volume variation (SVV) below 15%, and a MAP above 65 mmHg. If the CI^a will not be optimal, appropriate interventions will be performed to achieve optimal values.

In case of SVV>15%, a 250-ml bolus of crystalloid over 10 min will be administered. This process will be repeated until the SVV decrease below 15%. If the SVV is above 15%, and the CI^a decrease with administration of a bolus of crystalloid, inotropic therapy will be introduced (dobutamine) at a dose of 2,5 mcg/kg/min and increased if necessary to achieve CI^a>2,5 l.min.m−2

If hypotension occurs with MAP below 65 mmHg and SVV below 15%, norepinephrine therapy will be initiated.

After determining the optimal CI^a, we will aim to maintain the SVV below 15% to preserve the optimal CI^a. When the SVV exceed 15%, and the CI^a is lower than optimal, a crystalloid bolus (250 ml) will be administered. If, after administration of crystalloid, the SVV decrease below 15%, the CI^a will be verified. If the CI^a is optimal, no further action will be taken. If the CI^a remain suboptimal, the crystalloid bolus will be repeated.

If the SVV remain above 15% despite crystalloid bolus administration, the CI^a will be verified. If the CI^a increase, no further action will be taken. If the CI^a is suboptimal, inotropic therapy will be introduced (dobutamine).

In case of hypotension with MAP below 65 mmHg concurrent with an SVV above 15%, a 250-ml balanced crystalloid bolus will be administered. If hypotension with MAP below 65 mmHg and SVV below 15% occurs, norepinephrine therapy will be started.

Day 2

- Assessment of hemoglobin and plasma lactate level
- Recording blood loss and urinary output during and after surgery
- Transfusion products consumption
- Crystalloid and colloid solution consumption
- Monitoring of hemodynamic parameters except SVV
- Monitoring of adverse events and reactions including postoperative complications of special interest

Day 3 to Day 28 / ICU discharge (whichever comes first)

- Checking adverse events and adverse reactions (with special interest in postoperative complications of special interest)
- Discharge from ICU and hospital

Day 28

- Checking adverse events and adverse reactions (outpatient or telephone call)
- Mortality assessment

6.4. Biological samples

Blood samples will be taken following local practice and analysed in the respective clinical laboratory facility of the trial centre. No other biological specimens will be obtained or stored in this trial.

7. SAFETY ASSESSMENTS

Before the start of the clinical trial, all investigators will undergo training in pharmacovigilance requirements and procedures.

7.1. Definitions (according to the Regulation EU No. 536/2014)

For clinical trials, effective legislation has introduced the following definitions.

Table 2: Definitions of safety events

Adverse event	AE	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse drug reaction	ADR	All untoward and unintended responses to an investigational medicinal product related to any dose administered
Serious adverse event	SAE	A serious adverse event/reaction is any untoward medical occurrence or effect that at any dose: • **Results in death;** • **Is life-threatening;** • **Requires hospitalization or extension of existing hospitalization;** • **Results in persistent or significant disability or incapacity;** • **Is a congenital anomaly or birth defect.**
Serious adverse reaction	SADR	
Unexpected adverse reaction	UADR	Adverse reaction, the nature, severity, or outcome of which is not consistent with the product information (SmPC)
Suspected unexpected serious adverse reaction	SUSAR	Any suspected adverse reaction related to the study treatment that is both serious and unexpected.

7.2. AE surveillance, recording and documentation

AE could be diseases or symptoms which occur or worsen after the enrolment of a patient in the clinical trial. All AEs need to be documented, no matter if the investigator suspects a causal

connection to the study medication. AE will be monitored and documented **from the day of giving informed consent until the end of participation in the study** (i.e., End of Study Visit or Premature withdrawal Visit).

Subjects will be instructed to report any AEs that they experience to the investigator. The investigator should actively ask about AEs and record the potential AE.

Each AE should be described, documented in the eCRF, and evaluated to determine:

- Seriousness (see Chapter 7.4);
- Severity (see Chapter 7.5);
- Causality, i.e. relation to the study medication (see Chapter 7.6);
- Duration (start and end dates or whether it continues).
- Action taken (no action taken; study medication discontinued; prolongation of the ongoing hospitalization; administration of a drug etc.)

AE needs to be **followed until its resolution**, i.e. until it subsides, stabilizes, becomes chronic, or the subject dies.

If AE fulfils the criteria of **SAE**, **separate form in eCRF** must be completed (see Chapter 7.7).

AEs will be recorded according to the Medical Dictionary for Regulatory Activities (MedDRA). The most recent MedDRA version at the start of the study will be used.

7.3. Treatment of AE

A patient with an AE must receive appropriate therapy. The patient will remain under medical supervision until the investigator determines that the AE has been resolved.

7.4. Assessment of seriousness

AE is considered serious if it fulfils the definition in Chapter 7.1.

Some situations can be **considered as SAE even if they do not fulfil the criteria** of the definition. These are important medical events that may not be immediately life-threatening, or result in death, or hospitalization but may endanger the subject, or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered SAE – e.g., allergic bronchospasm, convulsions, or other states requiring treatment. If AE fulfils the criteria of SAE, a separate **Serious Adverse Event Form** have to be completed and sent to the sponsor. For the procedure see Chapter 7.7.

7.5. Assessment of intensity (severity)

The intensity (severity) of an AE should be evaluated according to these 5 categories:

Grade 1	AE is asymptomatic or mildly symptomatic, requires only observation, no medical intervention
Grade 2	AE with medium intensity, requires local, non-invasive, or small-scale treatment
Grade 3	AE is medically significant, requires hospitalization or extension of ongoing hospitalization, but it is not directly life-threatening

Grade 4	AE is life-threatening and requires urgent significant medical intervention
Grade 5	AE leads to death

7.6. Assessments of causality

To assess the relation between administration of the study medication and the AE, the following definitions apply:

- **Related** – The event is known to occur with the study medication, there is a reasonable possibility that the study medication caused the AE, or there is a temporal relationship between the study medication and AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study medication and the AE.
- **Not related** – There is not a reasonable possibility that the administration of the study medication caused the AE, there is no temporal relationship between the study medication and AE onset, or an alternate aetiology has been established.

7.7. Reporting of SAE and SUSAR

The investigator is obliged to report any SAE within 24 hours after he/she learns about it to the sponsor using Serious Adverse Event Form (SAE Form). The blank forms are stored in the Investigator's Site File. Reporting should be done by e-mail: farmakovigilance@med.muni.cz ***AND*** martina.kyselakova@med.muni.cz.

Sponsor will check the SAE Form completeness and formal plausibility. If required, queries will be made.

If all required information is not available at the time of the initial SAE report, follow-up reports should be sent by the investigator. Follow-up report should use a new blank SAE Form and the investigator should clearly state that this is a follow-up and give the date of the initial report. The investigator must update the SAE form and submit any supporting documentation (e.g., lab results, subject discharge summary, autopsy report) within 24 hours of receipt of this new information. The follow-up SAE report should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from trial participation.

All SAEs should be followed until their resolution, i.e., they subside, stabilize, become chronic, or the subject dies followed. In case of early termination because of SAE occurrence, the subject should be followed until SAE resolution. All necessary extra visits will be recorded in the eCRF as "Unscheduled visits".

In the case of death, a copy of the autopsy record should be added, if available. If the death of the subject complies with the definition of SUSAR (see Chapter 7.1), it will be reported as SUSAR (see below).

Sponsor has full responsibility for the safety of the clinical trial. Further reporting of AEs to the competent authorities according to the legal requirements is the responsibility of the sponsor.

Reporting of SUSAR

SAE related to the study medication fulfilling the criterion of unexpectedness (i.e., SUSAR) must be reported **by the sponsor** to the EudraVigilance database (module EVCTM), at the latest 15 days after it becomes known. Sponsor will also inform all Investigators involved in the trial. Reporting to the **EudraVigilance database** will be performed ***via* regulatory authority** according to the agreement between the sponsor and the regulatory authority. In case of a fatal or life-threatening SUSAR, the sponsor will report all relevant information immediately, at the latest 7 days after the event becomes known. Any subsequent additional information is forwarded within the next 8 days if necessary.

Person responsible for pharmacovigilance	**Deputy to the responsible person**
MUDr. Martina Kyseláková Tel: +420 778 517 417 E-mail: farmakovigilance@med.muni.cz E-mail: martina.kyselakova@med.muni.cz	MUDr. Kateřina Nerušilová Tel: +420 737 657 454 E-mail: farmakovigilance@med.muni.cz E-mail: nerusilova@med.muni.cz

7.8. Pregnancy

The Investigator should report the pregnancy to the Sponsor within 24 hours of learning of its occurrence using Pregnancy Form. This announcement will be done by e-mail: farmakovigilance@med.muni.cz ***AND*** martina.kyselakova@med.muni.cz.

Pregnancy and breastfeeding are exclusion criteria, and thus, pregnant and breastfeeding women cannot be included in the study. Pregnancy testing (hCG, urine sample) is obligatory at enrolment in women of childbearing potential[3]. Newly-emerged pregnancy in the hospitalization and follow-up phase of the trial is highly unlikely. However, if a subject becomes pregnant during the trial course, she must inform the investigator.

Pregnancy should be followed by the investigator until completion. If it ends for any reason before the anticipated date, the investigator should notify the sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for classification as SAE (e.g., spontaneous abortion, stillbirth,

[3] Childbearing potential is limited by the period from menarche to the onset of postmenopause (i.e. the period in which menstruation last occurred physiologically at least 12 months ago). The onset of postmenopause will not be verified by FSH testing, in case of doubt, the physician will consider the woman as a woman with childbearing potential.

neonatal death, postpartum complication, or congenital anomaly), the investigator should follow the procedures for reporting an SAE (see Chapter 7.7).

8. STATISTICS

A separate Statistical Analysis Plan (SAP) will be prepared to provide details on the approach to analyses. The SAP will be finalized before the database lock. All eventual deviations from the SAP will be described and justified in the relevant part of the Clinical Trial Report.

As a general approach for the descriptive analysis, the following statistics will be provided for continuous variables: number of subjects with available data (n), mean, standard deviation, median, 25% and 75% quartile, minimum and maximum. Categorical and binary variables will be presented as absolute and relative frequencies together with 95% CI, if appropriate.

For comparison between study arms two-sample Welch's t-test or its nonparametric alternative (Mann-Whitney test) will be used for continuous variables, Pearson's Chi-square test or Fisher exact test, if the assumptions for Chi-square test are not met, for categorical parameters.

Welch's t-test will be used if the normality is not rejected; otherwise Mann-Whitney test will be used for comparison of continuous variables. The normality will be checked visually (using histograms and Q-Q plots) and explored using Shapiro-Wilk test and eventually evaluated as a combination of visual assessment and statistical testing. If the normality of the data is not rejected, the difference between study groups will be expressed using difference between the means and 95% CI. Otherwise, the difference between the medians will be presented together with 95% CI calculated using bootstrap method.

As there is no formal statistical hypothesis to be tested, all statistical tests will be two-sided and performed on exploratory basis only. P-values < 0.05 will constitute statistically significant differences.

8.1. Sample size determination

A sample size of 140 participants (70 in each arm) was calculated to detect the difference between arms at two-sided type I error of 0.05 and power of 80% according to results of the pilot study [17]. Number of patients with any AESI was 33% in a control group and 11% in interventional group. A 10% dropout rate was already included in a total number.

8.2. Analysis of primary endpoint

The primary endpoint will be evaluated as number and percentage of patients with any AESI defined in section 2.2 and compared between study arms by Chi-square test or Fisher exact test. The difference between proportions including its 95% CI will be calculated as well.
FAS and PPS will be used for the analysis of the primary endpoint.

8.3. Analysis of secondary objective(s) and endpoint(s)

All secondary endpoints will be analysed using FAS. Descriptive statistics and statistical tests described above will be used based on the type of variables and fulfilment of criteria for the usage of particular tests.

The incidence of any adverse events and reactions will be analysed descriptively and compared between study arms in the same manner as the primary endpoint

Duration of surgery will be analysed descriptively and compared between study arms.

ICU and hospital length of stay (LOS) will be calculated as a number of days between admission and discharge, analysed descriptively and compared between study groups.

28-days mortality will be evaluated as a number and percentage of patients who are not alive 28 days after randomization and compared between study arms.

Hemodynamic characteristics, blood parameters (hemoglobin, plasma lactate level) and their changes over time will be analysed descriptively and compared between study arms.

Fluid balance and fluid therapy will be analysed descriptively and compared between study arms.

8.4. Demographic characteristics

Demographic characteristics of patients will be analysed descriptively overall and by study arms.

8.5. Missing data

In general missing data are not planned to be imputed. For secondary endpoints defined as duration (duration of surgery, ICU and hospital length of stay (LOS)) missing dates and/or times will be imputed based on the rules further specified in the SAP, unless missing due to premature discontinuation.

For the rest of continuous variables defined as secondary endpoints proportion of missing data will be evaluated, unless missing due to premature discontinuation. If more than 50% of the expected data are missing, imputation techniques might be applied within the scope of sensitivity analysis. Further details will be provided in the SAP.

8.6. Analysis sets

Full analysis set (FAS)
FAS comprises all randomized patients who underwent surgery. All endpoints will be evaluated using FAS.

Per-protocol set (PPS)
PPS includes all patients from FAS without protocol deviations which might affect the evaluation of primary endpoint. The principal investigator will assess protocol non-adherence on a case-by-case basis. Patients with significant deviations from the study protocol will be excluded from PPS.
PPS will be used for analysis of primary endpoint.

9. DATA MANAGEMENT AND QUALITY ASSURANCE

9.1. eCRF database

All participants will be assigned an identification code to ensure the pseudonymization of their data. The investigator will maintain a subject identification list for the trial centre (subject identification codes with the corresponding subject names) to enable records to be identified.

Trial data will be collected in eCRFs managed in electronic data capture system REDCap. Access to the database (username, password) will be granted by the study data manager, and the respective study staff will be trained for using it right and safely. The investigator is responsible for the data correctness, completeness, and filling in time. eCRF will be designed to generate queries on missing or unusual data in regular intervals.

The statistician will analyse the study data in cooperation with the principal investigator. The data will be stored for **25 years** after completion of the study and then destroyed.

9.2. Trial documents, medical records

The investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented. All essential paper documents are to be kept in the Investigator Site File (ISF) at the trial centre. Trial procedures, examinations and results must be described adequately in the patient's medical records, as well.

The sponsor, the trial site and study staff will handle the subject's personal and trial data according to the effective legislation regarding data protection. Any paper or electronic trial documents or data are confidential and must not be disclosed to the third persons. In the informed consent form, the participants are informed that their medical records can be provided only to the authorized monitors, auditors, or inspectors.

Medical records of the subjects will be kept in a legible form for **25 years** from the end of the clinical trial, as well as the relevant trial administrative documents at the sponsor's side.

9.3. Monitoring and auditing

The trial centre will be monitored according to the **Monitoring plan**. The objectives of the monitoring are to ensure that the trial participant's safety and rights are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and national legislation. Data in the eCRF will be reviewed and/or verified by the monitor during monitoring visits. Patient's medical records will serve as a source document for the verification.

The investigator agrees that the monitor will regularly visit the trial centre and will be given appropriate support (e.g., the access to all necessary documents incl. patient's medical records). A report on the progress, findings and resolution of any discrepancies will be prepared from each monitoring visit. The investigator undertakes to read the monitoring report and to ensure that any possible discrepancies are corrected. Sponsor, regulatory authority and ethics committees have the right to inspect/audit the trial site. The investigator undertakes to co-operate with the inspectors/auditors.

9.4. Steering committee

The Steering Committee is constituted by all study investigators of the NCHGDT trial. It is responsible for the development of the study protocol, continuous and final results interpretations and manuscripts preparation.

9.5. Medical monitoring

All ambiguous SAE or protocol deviations will be assessed by the investigator in consultation with the PhV manager and medical monitor of the study.

10. ETHICAL ASPECTS

This trial will be conducted following the applicable legislation and requirements for good clinical practice according to the ICH E6(R2). Compliance with this standard provides public assurance that the rights, safety, and well-being of trial participants are protected and that the clinical trial data are credible. All essential trial documents and their potential amendments will be submitted to the relevant ethics committee and regulatory authority for approval through CTIS.

10.1. Informed consent procedure

Consent will be acquired according to applicable legislation. Investigator will describe and discuss the content and course of the study with patients who also receive written information about the study. Adequate time will be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial. Investigator will obtain written consent from patients willing to participate in the trial. If trial subject is unable to sign the informed consent form because of medical condition, his or her legally designated representative after being duly informed of the nature of the study, may sign the consent. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness will sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative will be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent will be documented.

In case of patient´s inability to consent because of medical condition, the ability to participate in the study will be assessed by a medical council consisting of one independent physician informed of the study details and one study investigator. The informed consent has to be obtained from the patient as soon as possible when their medical condition improves, and they are able to sign the informed consent.

10.2. Supervision of the informed consent procedure

The process of obtaining informed consent from the subject, his or her legally designated representative or impartial witness, must always be properly documented by the investigator using valid forms as well as the patient's medical records. The clinical trial monitor will check

the process during monitoring visits. Important deviations in the process will lead to the termination of the patient's participation in the trial.

11. PUBLICATION POLICY

Results of this clinical trial are planned to be published in the medical literature. Any publications must be approved by the sponsor and meet the quality requirements for current clinical research publications (e.g., CONSORT statement).

12. FINANCING AND INSURANCE

NCHGDT is an investigator-initiated clinical trial. Financial resources will be provided from grant sources or Brno University Hospital project to support science and research. Investigators declare no financial or non-financial competing interest regarding the focus of this trial.

Mandatory insurance of the participants is arranged. The coverage for damages emerging from the participation in the clinical trial will be provided according to the applicable legal requirements.

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14. SUPPLEMENTS/APPENDICES

14.1. APPENDIX A AESI definitions

Acute kidney Injury	Defined according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines: Stage 1: serum creatinine 1.5–1.9 times baseline value within 7 days or ≥27 μmol l^{-1} (0.3 mg dl^{-1}) increase within 48 h; urine output ≤0.5 ml kg^{-1} h^{-1} for 6–12 h Stage 2: serum creatinine 2.0–2.9 times baseline value within 7 days; urine output ≤0.5 ml kg^{-1} h^{-1} for 12 h Stage 3: serum kreatinine 3.0 times baseline within 7 days or increase in serum creatinine to ≥354 μmol l^{-1} (≥4.0 mg.dl1 with an acute rise of > 44 mmol l^{-1} (0.5 mg/dl^{-1}) or initiation of renal replacement therapy or in patients < 18 years, decrease in eGFR to < 35 ml min^{-}1 per 1.73m2; urine output ≤0.3 ml kg1 h^{-1} for 24 h or anuria for 12 h
Acute Respiratory Distress Syndrome (ARDS)	The Berlin definition of Respiratory Distress Syndrome: Timing: Within one week of a known clinical insult or new or worsening respiratory symptoms and Chest imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse or nobles and Origin of oedema: Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor is presented and Oxygenation disorder: mild: PaO_2:FIO_2 between 26.7 and 40.0 kPa (200–300mmHg) with PEEP or CPAP ≥5 cmH_2O. Moderate: PaO_2:FIO_2 between 13.3 and 26.6 kPa (100–200 mmHg) with PEEP ≥5 cmH_2O. Severe: PaO_2:FIO_2 ≤13.3 kPa (100mmHg) with PEEP ≥5 cmH2O
Arrhythmia	Defined as electrocardiograph (ECG) evidence of cardiac rhythm disturbance. **Severity grading: ***
Cardiac arrest	Cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation.
Cardiogenic pulmonary oedema	Defined as evidence of fluid accumulation in the alveoli due to poor cardiac function. **Severity grading: ***
Deep vein thrombosis (DVT)	A new blood clot or thrombus within the venous system.

	Appropriate diagnostic tests include ultrasound, venography, CT or MRI venography. Plasma D-dimer measurement is not recommended as a diagnostic test in the first three weeks following surgery. **Severity grading: ***
Pulmonary embolism (PE)	A new blood clot or thrombus within the pulmonary arterial system.
Gastrointestinal bleed	Clinical or endoscopic evidence of blood in the gastrointestinal tract. **Severity grading: ***
Infection, source uncertain	Infection where there is strong clinical suspicion of infection but the source has not been confirmed because clinical information suggests more than one possible site, meeting two or more of the following criteria: core temperature < 36°C or >38°C; white cell count $>12\times10^9$ l^{-1} or $< 4\times10^9$ l^{-1}, respiratory rate >20 breaths per minute or PaCO2 < 4.7 kPa (35mmHg); pulse rate >90 beats per minute **Severity grading: ***
Laboratory confirmed bloodstream infection	Infection which meets at least one of the following criteria which should not be related to infection at another site: 1. Patient has a recognised pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site. 2. Patient has at least one of the following signs or symptoms: fever >38°C, chills or hypotension, and at least one of the following: a. Common skin contaminant cultured from two or more blood cultures drawn on separate occasions b. Common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy c. Positive blood antigen test. **Severity grading: ***
Myocardial infarction	Defined as increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria: symptoms of ischaemia; new or presumed new significant ST segment or T wave ECG changes or new left bundle branch block; development of pathological Q waves on ECG; radiological or

	echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality; identification of an intracoronary thrombus at angiography or autopsy. **Severity grading: ***
Pneumonia	Definition: Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease): (1) new or progressive and persistent infiltrates (2) consolidation (3) cavitation; at least one of the following: (1) fever (>38°C) with no other recognised cause (2) leucopaenia (white cell count < 4×10^9 l^{-1}) or leucocytosis (white cell count >12×10^9 l^{-1}) (3) for adults >70 years old, altered mental status with no other recognised cause; and at least two of the following: (1) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements (2) new onset or worsening cough, or dyspnoea, or tachypnoea (3) rales or bronchial breath sounds (4) worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand). **Severity grading: ***
Paralytic ileus	Failure to tolerate solid food or defecate for three or more days after surgery. **Severity grading: ***
Postoperative haemorrhage	Blood loss within 72 h after the start of surgery which would normally result in transfusion of blood. Severity grading: Mild: Not applicable. **Moderate**: Complication which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. **Severe:** Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Stroke	An embolic, thrombotic or haemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory). **Severity grading: ***
Brain oedema	Brain oedema confirmed on CT or MRI scan. **Severity Grading: ***
Surgical site infection (superficial)	A superficial incisional surgical site infection is defined as one which meets the following criteria:

	(1) Infection occurs within 30 days after surgery and (2) Involves only skin and subcutaneous tissue of the incision and (3) The patient has at least one of the following: (a) purulent drainage from the superficial incision (b) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision (c) at least one of the following symptoms or signs of infection: pain or tenderness, localised swelling, redness or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion. (d) diagnosis of an incisional surgical site infection by a surgeon or attending physician. **Severity grading: ***
Surgical site infection (deep)	A deep incisional surgical site infection as one which meets the following criteria: (1) Infection occurs within 30 days after surgery if no implant is left in place or 1 year if implant is in place. (2) Involves deep soft tissues (e.g. fascial and muscle layers) of the incision. (3) The patient has at least one of the following: (a) purulent drainage from the deep incision but not from the organ/space component of the surgical site (b) a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured when the patient has at least one of the following symptoms or signs: fever (>38°C), or localised pain or tenderness. A culture-negative finding does not meet this criterion. (c) an abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathological or radiological examination (d) diagnosis of an incisional surgical site infection by a surgeon or attending physician. **Severity grading: ***
Surgical site infection (organ/space)	Infection which involves any part of the body excluding the fascia or muscle layers and meets the following criteria: (1) Infection occurs within 30 days after surgery. (2) The infection appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia or

	muscle layers opened or manipulated during the operative procedure. (3) The patient has at least one of the following: (a) purulent drainage from a drain that is placed through a stab wound into the organ/space (b) organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space (c) an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathological or radiological examination (d) diagnosis of an organ/space surgical site infection by a surgeon or attending physician. **Severity grading: ***
Urinary tract infection	A positive urine culture of ≥10^5 colony forming units ml^{-1} with no more than two species of micro-organisms, and with at least one of the following symptoms or signs: fever (>38°C), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognised cause. Each of these criteria should be identified within a 24-h period. **Severity grading: ***

***Severity grading:**

Mild: Results in only temporary harm and would not usually require specific clinical treatment.
Moderate: More serious complication but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment.
Severe: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.