Individualized hemodynamic optimization guided by indirect measurement of respiratory exchange ratio in major surgery: study protocol for a randomized controlled trial (OPHIQUE study)

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Study protocol

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Abstract

Background

Observational studies have suggested that a high respiratory exchange ratio (RER) is associated with the occurrence of postoperative complications. The study's primary objective is to demonstrate that the incidence of postoperative complications is lower in an interventional group (patients monitored using a hemodynamic algorithm that incorporates the RER) than in a control group (treated according to standard practice).

Methods

We shall perform a prospective, multicenter, randomized, open-label, superiority trial of consecutive patients undergoing major non-cardiac surgery (i.e. abdominal, vascular and orthopedic surgery). The control group will be treated according to the current guidelines on standard hemodynamic care. The interventional group will be treated according an algorithm based on the RER. The primary outcome will be the occurrence of at least one complication within the 7 days following surgery. The secondary outcomes will be the length of hospital stay, the total number of complications per patient, 30-day mortality, the total intraoperative volume of fluids administered, the Sequential [sepsis-related] Organ Failure Assessment (SOFA) score, and laboratory data on postoperative days 1, 2 and 7. A total of 350 patients will be included.

Discussion

In the operating theater, the RER is potentially a continuously available, easy-to-read, indirect marker of tissue hypoperfusion and postoperative complications. If the RER predicts the occurrence of tissue hypoperfusion, it can help the physician to provide personalized hemodynamic management and limit the side effects related to excessive hemodynamic optimization (volume overload, vasoconstriction, etc.).

Trial registration

ClinicalTrials.gov identifier: NCT03852147. Registered on February 25th, 2019.

Administrative Information

Note

the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	**Individualized hemodynamic optimization guided by indirect measurement of respiratory exchange ratio in major surgery: study protocol for a randomized controlled trial (OPHIQUE trial)**
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Name and contact information for the trial sponsor {5b}	CHU Amiens-Picardie (Amiens University Medical Center). Clinical Research and Innovation Directorate F-80054 Amiens cedex 1 France
Role of sponsor {5c}	CHU Amiens-Picardie: management and analysis of data.

Introduction

Background and rationale {6a}

For many years, it was accepted that hemodynamic optimization during major noncardiac surgery was associated with lower rates of perioperative morbidity and mortality. This effect was based on maximization of blood flow (related to cardiac output (CO)), tissue perfusion (related to blood pressure), and thus oxygen delivery (DO_2) to the tissues [1]. Given that surgery is associated with an increase in oxygen consumption (VO_2), it can lead to a mismatch between DO_2 and VO_2; the body's metabolism becomes partially anaerobic, with tissue hypoperfusion and then postoperative complications [2]. In this context, the international guidelines now recommend hemodynamic optimization in major noncardiac surgery [3,4]. This approach is based on the use of fluids, vasopressors, and inotropic drugs. All these medications may trigger adverse reactions, which limit their benefits. Indeed, a few recent studies have not confirmed the clinical benefit of hemodynamic optimization [5–7]. Similarly, a recent meta-analysis found that hemodynamic optimization did not have medical benefit and was associated with adverse events (such as fluid overload) [8]. These results may have several explanations. Firstly, anesthesia procedures and surgical techniques have improved. Secondly, it has been suggested that hemodynamic optimization does not prevent the onset of anaerobic metabolism [5,8]. Anaerobic metabolism is thought to be triggered by an increase in VO_2 and a fall in DO_2. In such a case, all the determinants of DO_2 (the hemoglobin level, oxygen saturation, and CO) should be maximized to respond to the VO_2 demand. Thirdly, the POMO study demonstrated a beneficial effect of hemodynamic optimization only in patients who attained a VO_2 close to that measured preoperatively [5] - suggesting the need for individualized hemodynamic optimization. Fourthly, the postoperative morbidity essentially concerns patients with a low anaerobic threshold (an altered baseline VO_2), i.e. metabolically fragile patients for whom a DO_2 maximization strategy could be beneficial [8–10]. Taken as a whole, these results and observations suggest that the risk/benefit balance for hemodynamic management can only be achieved by personalized optimization in identified patients with baseline factors that favor anaerobic metabolism.

There is a large body of literature data on variables that can be used to diagnose and track the DO_2/VO_2 balance and changes in tissue perfusion. Most of these variables are derived from blood analyses. The results on the various parameters' ability to diagnose anaerobic metabolism are contradictory [11–15]. Based on the physiological knowledge of VO_2, DO_2, and CO_2 production (VCO_2), the respiratory quotient is known to be a non-invasive parameter reflecting the balance between DO_2 and VO_2 and thus anaerobic metabolism [16]. The respiratory quotient is widely used in physiology and cardiology. In the operating theatre, respiratory quotient can be approximated by measuring the respiratory exchange ratio (RER: the gradient between the inhaled/expired CO_2 and O_2 fractions and the minute ventilation). The RER reflects the body's energy metabolism and thus anaerobiosis [17]. In a model of hemorrhagic shock, changes in the RER reflect the mismatch between VCO_2 and VO_2 and thus anaerobic metabolism. Moreover, treatment of the shock corrected the RER [18]. We recently demonstrated that in major noncardiac surgery, the RER is predictive of hyperlactatemia and the occurrence of postoperative complications [19,20]. Thus, the RER may identify patients with VO_2/DO_2 mismatch and who might benefit from maximization of DO_2. Given the inhaled and exhaled fractions of O_2 and CO_2 are systematically measured in intubated-ventilated patients in the operating theater, the RER is readily available in all anesthetized patients. The RER might be an additional parameter for consideration in individualize hemodynamic management and might limit the adverse events associated with excessive hemodynamic optimization (volume overload) by selecting only patient who would be likely to benefit from this optimization strategy.

Thus, we hypothesized that individualized hemodynamic management based on continuous non-invasive measurement of the RER would lower the occurrence of postoperative complications because it provides information on the development of the VO_2/DO_2 imbalance, and limits excessive hemodynamic treatments.

Objectives {7}

The study's primary objective will be to demonstrate that a hemodynamic optimization algorithm based on the RER will lower the incidence of at least one postoperative complication (defined according to the European guidelines) in the 7 days following surgery.

The secondary objectives will be to demonstrate a decrease in the length of hospital stay, the incidence of each complication, the arterial lactate level at the end of the procedure and mortality at 30 days in patients RER group.

Trial design {8}

We are conducting a prospective, open-label, randomized, controlled, comparative, multicenter superiority study of two groups of patients (Figure 1).

Methods: Participants, Interventions And Outcomes

Study setting {9}

The study will take place in four university medical centers (Amiens University Medical Center, Lille University Medical Center, Caen University Medical Center, Dijon University Medical Center) and a general Hospital (Valenciennes General Hospital).

The list of study sites can be obtained from the Clinical Research and Innovation Directorate at Amiens University Medical Center (CHU Amiens- Picardie), F-80054 Amiens cedex 1, France.

Eligibility criteria {10}

1. Abdominal, orthopedic or vascular surgery with general anesthesia
2. Adult patients
3. American Society of Anesthesiology Physical Status score ≥II
4. Estimated duration of surgery >2 hours
5. At least two of the following co-morbidities: age >50, high blood pressure, cardiomyopathy, ECG abnormality, pulmonary edema, smoking, stroke, arteritis, insulin-dependent or non-insulin-dependent diabetes, ascites, chronic kidney failure.
6. Written consent

7. Affiliation with a social security scheme.

Non-inclusion criteria

1. Severe untreated arterial hypertension
2. Chronic renal failure on dialysis.
3. Acute heart failure.
4. Acute coronary syndrome.
5. Vascular surgery with renal plasty.
6. Cardiac surgery.
7. Permanent laparoscopy.
8. Preoperative acute circulatory failure
9. Refusal of patient participation.
10. Pregnant woman.
11. Patient under guardianship or curatorship or private of public law.
12. Anesthesia only with loco-regional technique (spinal and epidural anesthesia).
13. Acute respiratory distress syndrome (PaO_2/FiO_2 ratio < 300).
14. Chronic respiratory insufficiency with home oxygen therapy.
15. Patient included in another study.

Who will take informed consent? {26a}

All participants who meet the inclusion criteria during the study will be asked to participate in the study. The investigating physician will inform the patient about the study and will answer any questions concerning the study's objectives, constraints, foreseeable risks and expected benefits. He/she will also specify the patient's rights as part of this research and will check the eligibility criteria. Copies of the study information sheet and the consent form are then given to the patient by the investigating physician.

After patient has received this information, he/she will be given time to think about whether he/she wishes to participate. The investigating physician is responsible for obtaining the patient's written, informed consent. The consent form must be signed BEFORE ANY CLINICAL OR PARACLINICAL STUDY PROCEDURES are performed. If the patient agrees to participate, the patient and the investigator write their first and last names clearly and date and sign the consent form. The various copies of the study information sheet and the consent form are then distributed as follows:

A copy of the study information sheet and a copy of the signed consent forms are given to the patient.

The original copies are kept by the investigating physician (even if the patient moves during the course of the research) in a safe place that cannot be accessed by third parties.

At the end of the inclusion period or (at the latest) at the end of the research, a copy of each consent form shall be forwarded to the sponsor or its representative; the investigators will be told in a timely manner how these forms should be forwarded.

Additional consent provisions for collection and use of participant data and laboratory specimens {26b}

In the context of this research, no additional clinical or paraclinical examinations (i.e. beyond those normally applied for this type of surgery) will be performed.

Interventions

Explanation for the choice of comparators {6b}

In the control group, the patients' hemodynamic parameters are managed according to international and national guidelines by maintaining blood pressure with norepinephrine, optimizing the stroke volume by fluid challenge, and (if necessary) administering dobutamine [3,4] (Figure 2).

Cardiac output is optimized firstly by fluid challenge (maximization) and secondly (in the absence of preload dependency) by intravenous administration of dobutamine to obtain a cardiac index (CI) greater than 2.5 l min^{-1} m^{-2}. Dobutamine is administered via a dedicated peripheral venous access with an electric syringe pump. The dose of dobutamine (3 mg per kg bodyweight) is diluted in the syringe to give a total volume of 50 ml. The initial administration rate is 2.5 mL h^{-1} or 2.5 gamma kg^{-1} min^{-1}. If there is no change in the CI, the administration rate is increased in increments of 2.5 mL h^{-1} up to a maximum of 10 mL h^{-1} or 10 gamma kg^{-1} min^{-1}. The dobutamine infusion will be decreased if the heart rate rises above 100 bpm or increases by more than 40% of the baseline value.

The systolic arterial pressure (SAP) is maintained at more than 10% of the reference value by continuous intravenous administration of norepinephrine, if necessary. The mean initial infusion rate will be 0.05 µg/kg/min, and the infusion rate will be titrated to maintain the target SAP. The treatment is administered during the operative period only and begins with induction of anesthesia. Next, the targets are:

- A hemoglobin level greater than 10 g dl^{-1}, using blood transfusion.

- A pulse oxygen saturation (SpO_2) value greater than 95% using a recruitment maneuver, increased FiO_2 and titration of the positive end-expiratory *pressure* (Figure 2).

Intervention description {11a}

The RER is calculated from the continuous measurement of inspired and expired gases on the anesthesia ventilator (expressed in %): inspired fraction of oxygen (FiO_2), end-tidal fraction of oxygen ($FetO_2$), inspired fraction of CO_2 ($FiCO_2$) and end tidal fraction of CO_2 ($FetCO_2$), expired volume (Ve), and inspired volume (Vi). The value is averaged over a 5-minute moving window.

Assuming that Vi = Ve during mechanical ventilation in a closed circuit:

VCO_2 (ml.min^{-1}) = Ve x ($FetCO_2$-$FiCO_2$)

VO_2 (ml.min^{-1}) = Ve x (FiO_2 – $FetO_2$)

Thus:

RER = VCO_2 / VO_2 = ($FetCO_2$-$FiCO_2$) / (FiO_2-$FetO_2$)

An RER greater than 1.0 indicates anaerobic metabolism [19], and so DO_2 must be increased. This increase depends on the hemoglobin level, the arterial oxygen saturation, and the CO (Figure 2).

Cardiac output is optimized firstly by fluid challenge (maximization), and secondly (in the absence of preload dependence) by intravenous administration with dobutamine to obtain a CI greater than 2.5 l $min^{-1}m^{-2}$. Dobutamine is administered via an isolated peripheral venous access with an electric syringe pump. The dose of dobutamine is 3 mg per kg to be diluted in a syringe for a total volume of 50 ml. The starting rate of administration is 2.5 mL h^{-1} or 2.5 gamma kg^{-1} min^{-1}. If there is no change in the RER, the rate of administration is increased in steps of 2.5 mL h^{-1} up to a maximum of 10 mL h^{-1} or 10 gamma kg^{-1} min^{-1}. The dobutamine infusion is decreased if the heart rate rises above 100 bpm or by more than 40% of the baseline value.

Systolic arterial pressure is maintained at more than 10% of the reference value by the intravenous continuous administration of norepinephrine, if necessary. The infusion rate is initially set to 0.05 µg/kg/min and is then titrated to achieve the target SAP. The treatment is administered for the operating time only and begins with the induction of anesthesia.

Other objectives are:

- A hemoglobin level greater than 10 g dl^{-1}, using blood transfusion.

- A SpO_2 greater than 95% using a recruitment maneuver, increased FiO_2 and titration of the positive end-expiratory *pressure*.

If RER is lower than 1.0, systolic arterial pressure must be maintained at more than 10% of the reference value by the intravenous continuous administration of norepinephrine (Figure 3).

To both avoid extreme clinical practices and minimize interference with the trial intervention, study investigators will be strongly encouraged to apply standard measures, as follows:

- Induction of general anesthesia with the use of propofol 2-3 $mg.kg^{-1}$, sufentanil 0.2 $\mu g.kg^{-1}$ and cis-atracurium 0.15 $mg.kg^{-1}$. Inhaled anesthetics or target controlled infusion of propofol will be used to maintain general anesthesia with a target bispectral index of between 40 and 60, along with intravenous perfusion of sufentanil at 0.1 to 0.2 $\mu g.kg^{-1}$ per hour.

- Mechanical ventilation, with a tidal volume of 6-8 $ml.kg^{-1}$ predicted body weight, a positive end-expiratory pressure between 5 and 10 cmH_2O, a FiO_2 that maintains oxygen saturation ≥95%, and the respiratory rate adjusted to maintain an end-tidal CO_2 between 30-35 mmHg.

- Core body temperature maintained at 36.5°C.

- Peroperative use of epidural analgesia is allowed

- Postoperative epidural analgesia is authorized

Criteria for discontinuing or modifying allocated interventions {11b}

The study may be discontinued for an individual patient if the latter (or the person designated by the patient) so desires or if decided by the investigator Every effort will be made to comply with the study protocol. However, the clinician in charge of the patient may deviate from these instructions at any time if he/she considers it necessary. He/she must note this decision and the reason for it in the case report form. If the study is discontinued, no provision is made for patient replacement. Likewise, patients having discontinued the study for whatever reason will receive standard care for the surgery and disease in question.

Strategies to improve adherence to interventions {11c}

The coordinating investigator will ensure good adherence to the intervention via the following measures:

- Visits to study centers in order to train study staff in how to monitor the RER in the operating theater (readings, measurements, analysis, and the pathological threshold).
- Visits to study centers to explain the collection of primary and secondary outcomes and the follow-up visits (on post-operative day 1 (POD1), POD2, POD7, and POD30).
- The hemodynamic optimization protocol is identical to that used in routine care in the operating theater.
- Study centers will be regularly contacted by phone to ensure good compliance with the research protocol and so that any questions can be answered.

Throughout the hospital stay, it is the study team's responsibility to ensure the proper, timely assessment of outcome measures (including timely visits by the investigator).

Relevant concomitant care permitted or prohibited during the trial {11d}

The clinician in charge of the patient's care may deviate from these instructions at any time if he/she considers it necessary. He/she must notify this decision and the reason for it in the case report form. Both treatment groups have access to standard healthcare.

Provisions for post-trial care {30}

If the study is discontinued, no provision is made for patient replacement. Likewise, patients having discontinued the study for whatever reason will receive standard care for the surgery and disease in question.

Outcomes {12}

The primary study outcome is the occurrence of at least one complication within the 7 days following surgery. Organ failure is defined according to the guidelines issued by the European Society of Anaesthesia and the European Society for Intensive Care Medicine [21].

<u>Neurological complications:</u>

o Stroke, documented on CT.

o Mental confusion and disorientation in space and time, according to the Confusion Assessment Method for the ICU.

Respiratory complications:

- Acute respiratory distress syndrome (defined as polypnea >25/min, involvement of the accessory respiratory muscles or a pH <7.25), acute lung injury (defined as respiratory distress with a PaO_2/FiO_2 ratio <300 or a PaO_2 <80 mmHg under a high concentration mask), or adult respiratory distress syndrome (defined as respiratory distress with a PaO_2/FiO_2 ratio <200 mmHg).
- Pulmonary embolism, defined as the presence of one or more emboli in the arterial vessels of the non-operated lung when CT angioscopy is performed.
- Prolonged (>24 hours) orotracheal intubation.
- Repeated orotracheal intubation.

Cardiovascular complications:

- Acute systolic heart failure confirmed by echocardiographic impairment of the left ventricular ejection fraction from preoperative baseline.
- Acute right heart failure confirmed by echocardiographic impairment of right systolic and/or diastolic function.
- Acute pulmonary edema with fluid overload confirmed by a clinical examination and echocardiography and that leads to medical treatment.
- Acute circulatory insufficiency, defined as treatment with catecholamines (epinephrine, dobutamine, phosphodiesterase inhibitor, levosimendan, and norepinephrine).
- Postoperative myocardial damage: troponin I or T elevation above the 99^{th}
- Myocardial infarction, defined as an elevation in cardiac enzymes (CPK-MB, troponin T, or troponin I) plus the appearance of a new Q-wave, ST-segment elevation or ECG repolarization disorder.
- Supraventricular rhythm disorders, defined as the occurrence of atrial flutter or complete arrhythmia by atrial fibrillation and confirmed by ECG.
- Ventricular rhythm disorders, defined as the occurrence of ventricular tachycardia, confirmed by ECG.

Acute renal failure, defined as a postoperative increase of at least 50% and/or 26.5 µmol/l in the creatinine level vs. the preoperative baseline and/or diuresis of less than 0.5 ml kg^{-1} h^{-1} over 6 hours (the KDIGO International Society of Nephrology definition) [22].

Digestive complications:

- Mesenteric ischemia/ischemic colitis documented by CT and/or colonoscopic and/or surgical imaging.
- Digestive tract hemorrhage (upper or lower) defined as the occurrence of hematemesis, melena or rectorrhagia.
- Post-operative ileus, defined as a transitory (>48 hours) halt or slowing of intestinal transit.

Hemorrhagic complications:

- Post-operative bleeding.
- Disseminated intravascular coagulation.
- Transfusion with blood derivatives: red blood cells, platelets, and fresh plasma.
- Inflammatory systemic response syndrome, defined as the presence of at least two of the following criteria: (i) body temperature <36°C or >38°C; (ii) heart rate >90 beats/min; (iii) Respiratory rate >20 cycles/min or a $PaCO_2$ <32 mmHg in a blood gas analysis; and (iv) leukocyte count < $4000/mm^3$ or $>12000/mm^3$.

Infectious complications:

- Surgical site infection, defined as the occurrence of wall infection (abscess or purulent discharge) or a documented bacterial infection.

- Symptomatic or asymptomatic post-operative urinary tract infection, defined as the presence of a germ (>10^5 CFU/mm^3) in the urine.
- Pneumopathy, defined as new lung infiltrates plus at least two of the following: (i) Fever >38.5°C or hypothermia < 35.5°C; (ii) Leukopenia < 4,000 GB/mm^3 or hyperleukocytosis >12,000 GB/mm^3; (iii)
- Purulent secretions. Bacteriological confirmation will be made by the presence of microorganisms in bronchial samples (sputum culture >10^7 CFU/mm^3, bronchial aspirate >10^5 CFU/mm^3, bronchoalveolar lavage >10^4 CFU/mm^3, distal protected aspirate or protected specimen brush >10^3 CFU/mm^3).
- Bacteremia, defined as the presence of a positive blood culture for a pathogenic germ.
- Infection of a catheter (central venous or arterial), defined as a positive culture of the same microorganism on the catheter (>10^3 CFU ml^{-1}) and in at least 1 peripheral blood sample.
- Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical application, organ dysfunction can be represented as an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality rate above 10%.
- Septic shock, defined as a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than for sepsis alone. Patients with septic shock can be clinically identified by the requirement for vasopressor to maintain a mean arterial pressure (MAP) of >65 mmHg and a serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia [23].

Death during hospitalization, at post-operative day (POD) 30, and at one year. Each patient's vital status will be documented via a telephone call 30 days after surgery.

The secondary outcomes are:

- Length of stay: length of stay in intensive care (the number of days spent in post-operative intensive care) and overall length of stay in hospital (the number of days spent in hospital until discharge).
- The total number of complications per patient.
- Mortality on POD30.
- Total intraoperative IV fluids administered (crystalloids and colloids).
- Laboratory criteria and the SOFA score: plasma creatinine, lactate, C-reactive protein (CRP), troponin Tc, and brain natriuretic peptide (BNP) measured at D1, D2 and D7 postoperatively.

Participant timeline {13}

The inclusion period is expected to last for 48 months. Several visits are provided for in the protocol. The visits take place when the patient is hospitalized, on the day of inclusion/surgery (POD0), POD1, POD2, POD7, and POD30 (Figure 1). The visits on POD0, POD1, POD2, and POD7 must be performed on the scheduled day. For the visit on POD30, a margin of 5 days before D30 and 5 days after D30 will be tolerated.

THE PRE-INCLUSION (ENROLLMENT) VISIT

The pre-inclusion visit must be carried out by an investigator named in the protocol. It will take place during the pre-anesthesia consultation (PAC). All selected patients meeting all the inclusion criteria and none of the non-inclusion criteria will be invited to participate in the study. The investigating physician will inform the patient about the study and will answer any questions concerning the study's objectives, constraints, foreseeable risks and expected benefits. He/she will also specify the patient's rights as part of this research and will check the eligibility criteria. Copies of the study information sheet and the consent form are then given to the patient by the investigating physician. After patient has received this information, he/she will be given time to think about whether he/she wishes to participate. The investigating physician is responsible for obtaining the patient's written, informed consent. The consent form must be signed BEFORE ANY CLINICAL OR PARACLINICAL STUDY PROCEDURES are performed. However, in the context of this research, no additional clinical or paraclinical examinations (i.e. beyond those normally applied for this type of surgery) will be performed.

If the patient agrees to participate, the patient and the investigator write their first and last names clearly and date and sign the consent form.

ALLOCATION

The patients will be randomized by an investigator named in the protocol. After checking the patient's inclusion criteria and consent, the investigator connects to the secure (SSL) website https://recherche-clinique.chu-amiens.fr/CSOnline/ and creates a patient file in the database (assignment of the patient code). The investigator will have to enter the requested data in order to check the inclusion and non-inclusion criteria. If all the requested data are entered and are consistent, the investigator will be given the result of the randomization as either "standard management" or "respiratory exchange ratio". If any of the data are erroneous or data, an error message will indicate which corrections must be made so that the patient can be randomized.

FOLLOW-UP VISITS

Five follow-up visits are planned: on the day of inclusion/surgery (POD0), POD1, POD2, POD7, and POD30. The visits on POD1, POD2, POD7 and POD30 are performed by an anesthesiologist who is blinded to the group allocation and has not managed the patient in the operating theater. These visits enable the progressive, consecutive collection of the study data.

Participation in the study will not change how patients are managed during their stay in the intensive care unit and in hospital generally, other than compliance with the hemodynamic optimization protocol. As part of their care, patients always provide several blood samples - including at least one per day during the first week.

END-OF-STUDY VISIT

The end-of-study visit takes place on POD30. The purpose of this visit is to collect study data generated since the previous visit (POD7). The variables documented will be the same as those document at the POD7 visit. The end of the study is defined as the last study visit by the last person participating in the study. No particular post-study treatments are planned for study participants.

Study timeline for participants.

	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT			***POD1***	***POD2***	***POD7***	***D30***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Sign consent form	X					
Allocation		X				
INTERVENTIONS:						
Intervention group						
Control group						
ASSESSMENTS: ***Baseline Data:*** _ Demographic data _ Medical history _ Operative indication _ Preoperative laboratory assessment _Drug treatments	X					
Primary outcome			X	X	X	X
Secondary outcomes			X	X	X	X

Sample size {14}

According to the literature data, the postoperative complication rate in the target population is between 30% and 50% [24]. The inclusion of 170 patients in each arm would show that RER-based hemodynamic optimization reduces these complications in a clinically significant manner (by a third; from 50% in the control group to 35% in the experimental arm). These calculations were performed with an alpha risk of 5%, a power of 80%, and a complication rate of 50% in the control arm.

Furthermore, an interim analysis is planned halfway through the inclusion process. Hence, the final study population should be 344 patients. On the basis of these results and after taking account of patients who are not evaluable, we plan to include 350 patients (175 per arm). If 175 patients are included in each arm, the threshold for statistical significance in a one-sided test will be set to $p<0.003$ (according to the Lan and Demets spending function, using the seqdesign SAS procedure). Premature study termination for efficacy could thus be considered.

Recruitment {15}

The feasibility of this project is guaranteed by (i) the relatively large number of potentially eligible patients treated in the various centers, and (ii) the involvement of a multicenter group whose members have been working together on hemodynamic optimization research projects for many years.

Number of eligible patients per center:

Amiens University Medical Center: 2 to 3 inclusions per month

Lille University Medical Center: 1 inclusion per month

Caen University Medical Center: 1 inclusion per month

Dijon University Medical Center: 2 to 3 inclusions per month

Valenciennes General Hospital: 1 inclusion per month

Assignment of interventions: allocation

Sequence generation {16a}

Patients will be randomized into the two parallel, open-label groups using Clinsight® software, as implemented by a data manager from the Clinical Research and Innovation Directorate at Amiens University Medical Center. Randomization by minimization will be performed.

The randomization will be stratified:

- by center.

- by the type of surgery (orthopedic, vascular, or abdominal).

Patients will be randomly assigned to one of the study groups via centralized randomization by minimization in order to better check for stratification factors and to balance the size of the groups. This will also make it possible to check patient eligibility and send randomization information to the investigator for each patient.

After entering their username and password, the investigators will connect to the study randomization site on the day of inclusion and check the inclusion and non-inclusion criteria. If no inconsistencies are found, the result of the randomization will be displayed as "standard management" or "respiratory exchange ratio".

Concealment mechanism {16b}

Prior to the provision of informed consent, participants (and, if applicable, their legal guardians) will be given full information about the study by the researchers at each study site. The provision of study information will be recorded in the Clinsight® software by the research assistants. After the baseline survey, eligible participants will be randomized 1:1 into two groups.

Implementation {16c}

The pre-inclusion visit is carried out by an investigator named in the protocol. It will take place during the PAC. All selected patients meeting all the inclusion criteria and none of the non-inclusion criteria will be invited to participate in the study.

Patient information and consent

The investigating physician will inform the patient about the study and will answer any questions concerning the study's objectives, constraints, foreseeable risks and expected benefits. He/she will also specify the patient's rights as part of this research and will check the eligibility criteria. Copies of the study information sheet and the consent form are then given to the patient by the investigating physician.

After patient has received this information, he/she will be given time to think about whether he/she wishes to participate. The investigating physician is responsible for obtaining the patient's written, informed consent. The consent form must be signed BEFORE ANY CLINICAL OR PARACLINICAL STUDY PROCEDURES are performed. However, in the context of this research, no additional clinical or paraclinical examinations (i.e. beyond those normally applied for this type of surgery) will be performed.

If the patient agrees to participate, the patient and the investigator write their first and last names clearly and date and sign the consent form. The various copies of the study information sheet and the consent form are then distributed as follows:

A copy of the study information sheet and a copy of the signed consent forms are given to the patient.

The original copies are kept by the investigating physician (even if the patient moves during the course of the research) in a safe place that cannot be accessed by third parties.

At the end of the inclusion period or (at the latest) at the end of the research, a copy of each consent form shall be forwarded to the sponsor or its representative; the investigators will be told in a timely manner how these forms should be forwarded.

Assignment of interventions: blinding

Who will be blinded {17a}

Although the operating anesthetists cannot be blinded to group assignments, much attention will be given to ensuring strict blinding during the post-operative, data collection, and data analysis periods. The surgeons, ICU physicians and nurses are blinded to group allocation. Only the anesthetist in charge of the patient during the surgery will be aware of the group allocation.

Procedure for unblinding if needed {17b}

Unblinding procedure is not necessary, and not planned.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All data will be continuously recorded on a case report form by a clinical data manager who is blinded to the group allocation. All the information required by the protocol must be recorded as and when it is obtained in the electronic case report form and any missing data must be explained:

- “NK” for “not known”
- “ND” for “not determined”
- “NA” for “not applicable”.

Any access to the study data and any changes will be tracked via the Clinsight® software (Ennov Clinical).

- Preoperative data:

¬ Demographic data

¬ Medical history (high blood pressure, diabetes, kidney failure), indication for surgery (neoplastic disease or not)
¬ Preoperative laboratory assessment (including plasma creatinine and CRP levels)

¬ Drug treatments (antihypertensive drugs, antidiabetics, diuretics, etc.)

- Intraoperative data

¬ Anesthetic data:

- Hypnotics, opioids and muscle relaxants used
- Volume of fluids used (crystalloids and colloids)
- Number of labile blood products used

- Hemodynamic data (every 30 minutes):

¬ SAP, DAP and mean AP

¬ Heart rate

¬ Bispectral index

¬ Temperature
¬ CO

¬ Pulse pressure variation
¬ Total amount of ephedrine and norepinephrine hydrochloride used
¬ Total amount of dobutamine
¬ Intraoperative diuresis

- Surgical data:
¬ Surgical indication and type of surgery (abdominal, vascular or orthopedic)
¬ Duration of surgery
¬ Volume of blood loss
¬ Intraoperative surgical complications

- Postoperative data
¬ Length of stay in the recovery room
¬ Patient discharge (to a surgical department, intensive care unit or the recovery room)
¬ Laboratory assessment:
- Kidney function: serum creatinine and urea on POD1, POD2, POD7, renal replacement therapy
- Laboratory assessment on POD1, POD2 and POD7 (blood lactate and plasma creatinine, CRP, BNP and troponin Tc)
¬ Usual clinical data (heart rate, blood pressure, peripheral O_2 saturation, and respiratory rate)
¬ Diuresis on POD1, POD2 and POD7
¬ KDIGO scores on POD1, POD2 and POD7
¬ Postoperative complications
¬ Length of stay in intensive care and in hospital

¬ 30-day post-operative mortality

Plans to promote participant retention and complete follow-up {18b}

At each visit participants will be reminded of the importance of their participation in the study and the need to be continuously contactable and available for monitoring until the end of the follow-up period. We will make sure that appointments for study visits at different times of day and on different days of the week are available. Saturday visits will also be available for participants who cannot attend during the week.

Participants who withdraw from the trial will be contacted (with their prior permission) by phone on POD30 in order to check on whether they developed postoperative complications.

Data management {19}

All data will be continuously recorded on a case report form by a clinical data manager who is blinded to patient allocation. Data collected directly during the patient's follow-up will be entered (single-entry) into an electronic case report form by the principal investigator (or by authorized persons referenced on the task delegation list) on the https://recherche-clinique.chu-amiens.fr/CSOnline/ website.

The pre-configured consistency tests will check the quality of the data. If inconsistencies are detected, queries will be sent to the investigator.

The data coding will be given on a separate sheet within the electronic case report form. Data will be entered initially as the actual numerical value or the actual categorical variable.

At the end of the study, the Clinsight® database (Ennov Clinical) will be frozen by a data manager at Amiens University Medical Center's Clinical Research and Innovation Directorate. The centralized data will then undergo statistical analysis using SAS® software (version 9.4).

Confidentiality {27}

In accordance with the legislative provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Code), people with direct access to source data will take all the necessary precautions to ensure the confidentiality of information relating to the study drugs, research, participants (particular the latter's names) and results. Like the investigators, these people are subject to a professional duty of confidentiality.

During or after the study, the data collected on the participants will be sent to the sponsor by the investigators (or any other specialist staff) will be pseudonymized. They must in no case show the study participants' names or address.
Data confidentiality will be ensured by coding the participants' information as follows:
- the participant's initials: the first letter of the family name and the first letter of first name.
- a 5-digit code number: the first two digits corresponding to the center number and the final three digits correspond to the incremental inclusion number (from 001 upwards).

The sponsor will ensure that each study participant has given his/her written consent to access to his/her personal data required for the study's quality control procedures.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The study's primary objective is to demonstrate that the incidence of postoperative complications is lower in an interventional group (patients monitored using a hemodynamic algorithm that incorporates the RER) than in a control group (treated according to standard practice).

To summarize the characteristics of the study population, quantitative variables will be described as the mean ± standard deviation and the median [interquartile range]. Qualitative variables will be described as the frequency [95% confidence interval].

Analysis of the primary outcome:

The null hypothesis will be rejected in favor of the alternative hypothesis (i.e. there is a difference) using a chi-squared test or Fisher's test, depending on the frequency of complications ($n<5$ in a cell of the contingency table), with a two-sided alpha risk of 5%.

Analysis of the secondary outcome:

The two arms will be compared with regard to the total volume of intraoperative fluids and the length of stay, using Student's test or the Mann-Whitney test for normally distributed data.

The two arms will be compared with regard to the changes over time in the SOFA score and the NT-pro-BNP, troponin TC, CRP, lactate and creatinine levels using a mixed-model analysis of variance. Post-hoc comparisons will be performed after adjustment with Hochberg's method. If the data are not normally distributed, they will be log-transformed or otherwise transformed.

The intergroup difference in the incidence of each complication (including mortality) will be compared with in a chi-squared test or Fisher's test.

All statistical analyses will be performed using SAS® software (version 9.4, SAS Institute Inc., Cary, NC, USA). The threshold for statistical significance will be set to $p<0.05$ for both the primary and secondary outcomes. The statistical criteria for premature termination of the study are listed above in the statistical analysis section ($p<0.003$).

Interim analyses {21b}

An interim analysis is planned half way through the inclusion process (n=175 out of 350).

Methods for additional analyses (e.g. subgroup analyses) {20b}

No additional analyses are planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

For the primary outcome, we expect the proportion of missing data to be below 5%. We will not perform multiple imputations for the primary outcome unless more than 5% of the data are missing.

The secondary outcomes will be assessed in the full analysis set.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The full protocol is available from ClinicalTrials.gov (Identifier: NCT03852147. February 25, 2019)

Participant-level data and statistical code are available on request from the Clinical Research and Innovation Directorate at CHU Amiens-Picardie.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

Sponsor:

CHU Amiens-Picardie

Clinical Research and Innovation Directorate

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Tel.: +33-322-088-371; Fax: +33-322-089-645

Methodology and Data Monitoring Committee:

Momar DIOUF, Biostatistician

Pauline MORIN, Data Manager

Salah MATTOUG, Project Manager

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Composition of the data monitoring committee, its role and reporting structure {21a}

Data Monitoring Committee:

Momar DIOUF, Biostatistician

Pauline MORIN, Data Manager

Salah MATTOUG, Project Manager

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France

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Adverse event reporting and harms {22}

The investigator assesses each adverse event in terms of its seriousness. The investigator should notify the sponsor without delay from the day on which he/she becomes aware of any serious adverse event or new development, if it occurs:

- after the date on which the consent form is signed.

- during the patient's follow-up period.

All these events must to be monitored until they have completely resolved. Additional information (on a supplementary reporting form) concerning the progression of the event (if not mentioned in the first report) will be sent to the sponsor by the investigator.

The sponsor/Vigilance Unit will report developments in the study in a timely manner to:

- the French Agency for Health Product Safety (ANSM).

- the competent institutional review board (IRB). If necessary, the IRB will check that the study participants have been informed of the adverse effects and have not withdrawn their consent.

1. In the case of an unexpected serious adverse reaction resulting in death or endangerment of life, without delay from the day on which the sponsor becomes aware of it.
2. In the case of other unexpected serious adverse effects, no later than two weeks from the day on which the sponsor became aware of them.

The sponsor shall report relevant additional information on unexpected serious adverse reactions in the form of a follow-up report to the ANSM. In the case of a suspected unexpected serious adverse reaction resulting in death or life-threatening injury, this additional information shall be notified within a week of the report mentioned in (1). In the other cases of a suspected serious unexpected adverse effect and if new information (as defined in Article L.1123-10) has emerged, the relevant additional information is transmitted within a further week of the deadline mentioned in (2).

If necessary, the IRB will check that the study participants have been informed of the adverse effects and have not withdrawn their consent. The sponsor and the investigator shall take appropriate urgent action. The sponsor shall inform the competent authority and the IRB.

On the anniversary date of the first inclusion, the sponsor shall draw up a safety report, including (i) a list of serious adverse events that may be related to the research (including expected and unexpected serious events), and (ii) a concise, critical analysis of the safety of study participants.

This report shall be sent to the ANSM and the IRB within 60 days of the anniversary date of the first inclusion.

Frequency and plans for auditing trial conduct {23}

A clinical research associate mandated by the sponsor visits each center at the time the study is set up, one or more times during the study (depending on the inclusion rate), and at the end of the research. During these visits, the following elements will be reviewed: informed consent, compliance with the research protocol and the procedures defined therein, quality of the data collected in the electronic case report form, accuracy, missing data, consistency of data with source documents (medical records, appointment books, original laboratory results, etc.), and management of any products.

A written monitoring report will be required after each visit.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any protocol amendments must be authorized by the IRB prior to implementation. The IRB will be informed of non-substantial amendments (i.e. those that do not have a significant impact on any aspect of the research).

Prior to submission to the IRB, all amendments are to be validated by the sponsor and by all research stakeholders affected by the amendment. All amendments to the protocol must be made known to all investigators participating in the study. The investigators undertake to comply with the protocol. Any amendment that modifies patient management or the study's benefits, risks and constraints requires a new study information sheet and a new consent form, to be processed according to the above-mentioned procedure. The following study documents will be archived in accordance with good clinical practice.

- By the investigating physicians

- For a period of 15 years after the end of the study (for studies related to medicines, medical devices or *in vitro* diagnostics, or for studies not related to a product mentioned in Article L.5311-1 of the French Public Health Code):

- The protocol and any amendments.

- Case report forms (copies).

- Source files for study participants having given their written consent.

- All the other documents and correspondence related to the research

- For a period of 30 years after the end of the study.

- The participants' original signed informed consent forms.

All these documents are under the responsibility of the investigator for the prescribed archiving period.

- By the promoter

- for a period of 15 years following the end of the study (for studies related to medicines, medical devices or *in vitro* diagnostics, or for studies not related to a product mentioned in Article L.5311-1 of the French Public Health Code).

- *not applicable*

- For a period of 30 years after the end of the study.

- Copies of the participants' original signed informed consent forms.

- Documents concerning serious adverse events.

All such documents are the sponsor's responsibility for the legally stipulated period of archiving.

No documents are to be removed or destroyed without the sponsor's agreement. At the end of the legally stipulated period of archiving, the sponsor will be consulted prior to destruction of the documents. All data, documents and reports may be subject to audit or inspection.

Dissemination plans {31a}

The data provided by the investigative centers will be analyzed by a biostatistician from the Clinical Research and Innovation Directorate at Amiens University Medical Center. This analysis will give rise to a written report submitted to the sponsor, who will forward it to the IRB and to the competent authority.

Any written or oral communication of the results of the research must be first be approved by the principal investigator and, where appropriate, any committee set up for the purposes of the study.

The publication of the principal results will mention the name of the sponsor, all investigators who included or followed up patients in the research, and the methodologists, biostatisticians and data managers who participated in the research. The international rules for writing and publication will be taken into account (The Uniform Requirements for Manuscripts of the ICMJE, April 2010). In accordance with the French Parliamentary Act 2002-303 dated March 4th, 2002), the study participants will be informed (on request) of the study's overall results.

Discussion

In the operating theater, the RER is potentially a continuously available, easy-to-read, indirect marker of tissue hypoperfusion and postoperative complications. In contrast to conventional tissue perfusion variables, the RER does not require repeated, invasive measurements of venous and arterial blood gas levels; indeed, the repetition of blood gas measurements may decrease reproducibility. Since the RER can diagnose patients with DO_2/VO_2 mismatch, it enables personalized hemodynamic management and thus may limit the side effects due to excessive hemodynamic optimization (volume overload, vasoconstriction, etc.). Thus, the RER might help to tailor hemodynamic optimization to each patient as a function of the type of surgery and the metabolic requirement. If this approach works, the RER could be used in routinely in the operating theater to improve the management of patients undergoing major surgery.

One limitation of the present study is that the operating anesthetists are not blinded to the group assignments. Hence, we have given much attention to strict blinding during the post-operative, data collection and data analysis periods. The surgeons, ICU physicians, and nurses are blinded to group allocation. Only the anesthetist in charge of the patient during the surgery knows the group allocation. Moreover, this is the first large, randomized controlled trial of the effectiveness of the RER in the operating theatre.

Trial Status

This is protocol version 1.6, dated March 3rd, 2020. Recruitment started on December 26th, 2018. To date, 120 participants have been randomized. The estimated date for the completion of recruitment is January 2023.

Abbreviations

ANSM
French Agency for Health Product Safety
AP
arterial pressure

CI
cardiac index
CO
cardiac output
DAP
diastolic arterial pressure
DO_2
arterial oxygen delivery
$FetO_2$
end-tidal fraction of oxygen
$FetCO_2$
end-tidal fraction of CO_2
FiO_2
inspired fraction of oxygen
$FiCO_2$
inspired fraction of CO_2
MAP
mean arterial pressure
PAC
pre-anesthesia consultation
RER
respiratory exchange ratio
SAP
systolic arterial pressure
SpO_2
pulse oxygen saturation
SOFA
Sequential [Sepsis-related] Organ Failure Assessment
VCO_2
CO_2 production
VO_2
oxygen consumption

Declarations

Acknowledgements

Not applicable.

Authors' contributions {31b}

SB is the lead investigator; SB and PGG conceived the study and led the development of the proposal and the protocol; EL, HD and MOF contributed to study design and to development of the proposal; PB, YEA, RD, MM and OAA drafted the manuscript. All authors read and approved the final manuscript.

Funding {4}

The trial was funded by the French government's Interregional Hospital-Based Clinical Research Program (*Programme Hospitalier de Recherche Clinique (PHRC) Inter-régional GIRCI Nord-Ouest 2017* (API17-03). The funding body had no role in writing the manuscript and will not have any role in study execution, the collection, management, analysis or interpretation of data, or the decision to submit results.

Availability of data and materials {29}

Data will be available on request from the Clinical Research and Innovation Directorate at CHU Amiens-Picardie.

Ethics approval and consent to participate {24}

The study was approved by the local IRB (CPP Ile de France II; reference: ID-RCB/ EUDRACT: 2018-A00593-52). It was registered at ClinicalTrials.gov (NCT03852147) on February 25th, 2019, and is being conducted in accordance with the Declaration of Helsinki on ethical principles for medical research involving human subjects. Study participation is voluntary, and each participant will be comprehensively informed about the objectives of the study, the privacy policy, and the opportunity to withdraw from the study at any time without stating a reason. Each study participant will provide his/her written, informed consent to participation and a data privacy from. Each participant will receive a copy of his/her informed consent form.

Consent for publication {32}

Information on the participants' consent for publication is available from the corresponding author on request.

Competing interests {28}

The authors declare that they have no competing interests.

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Figures

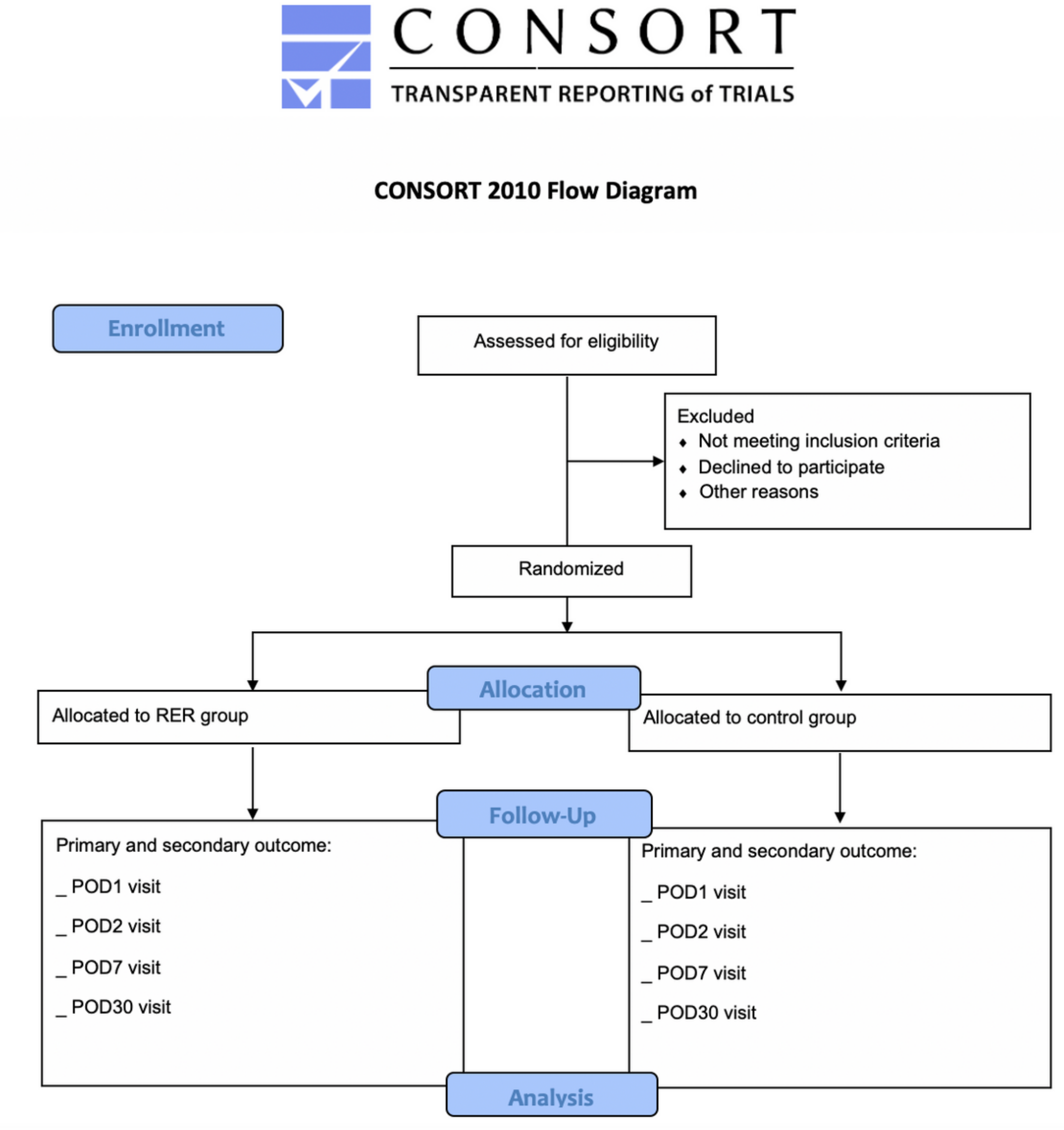

Figure 1

CONSORT flow diagram.

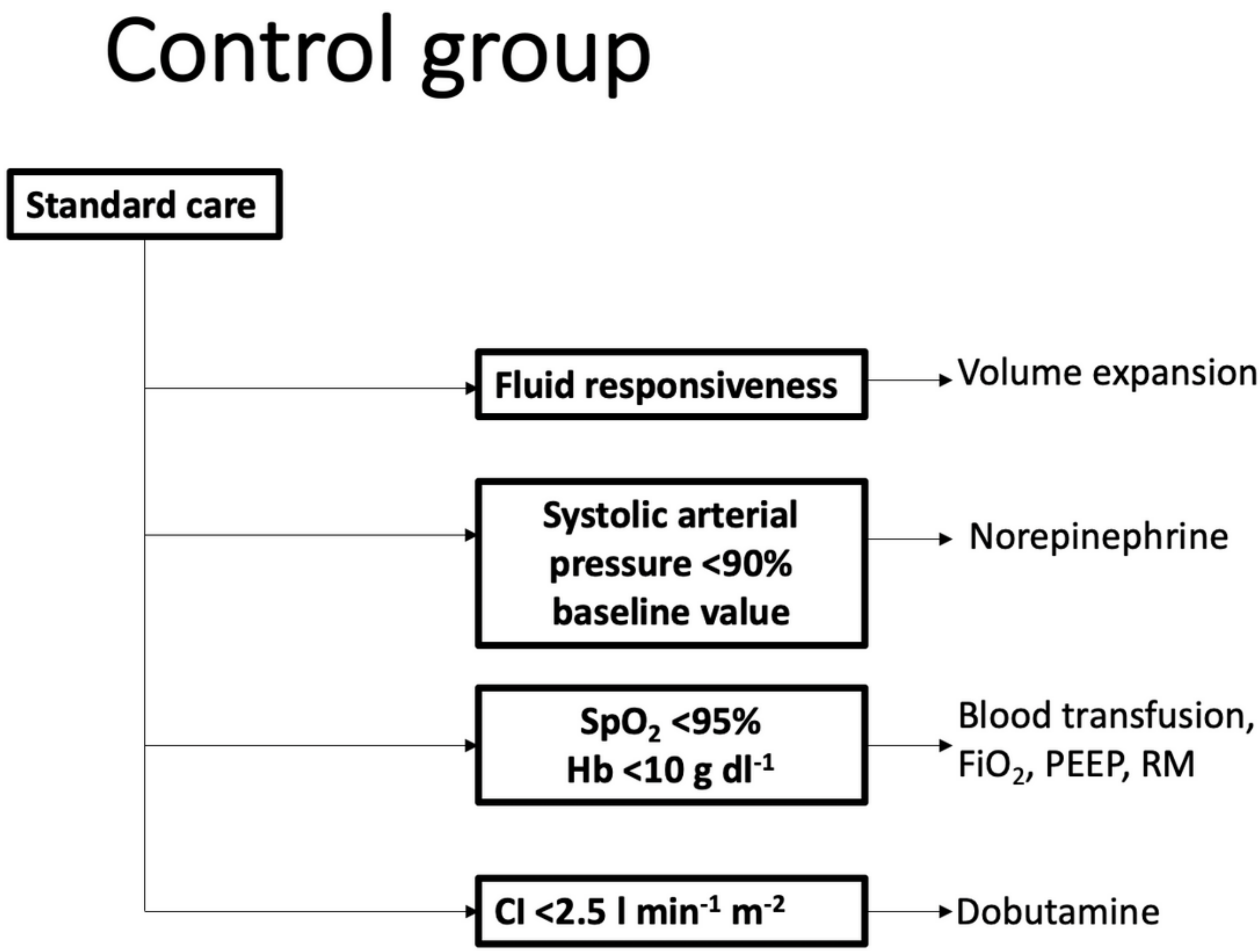

Figure 2

Algorithm for management in control group.

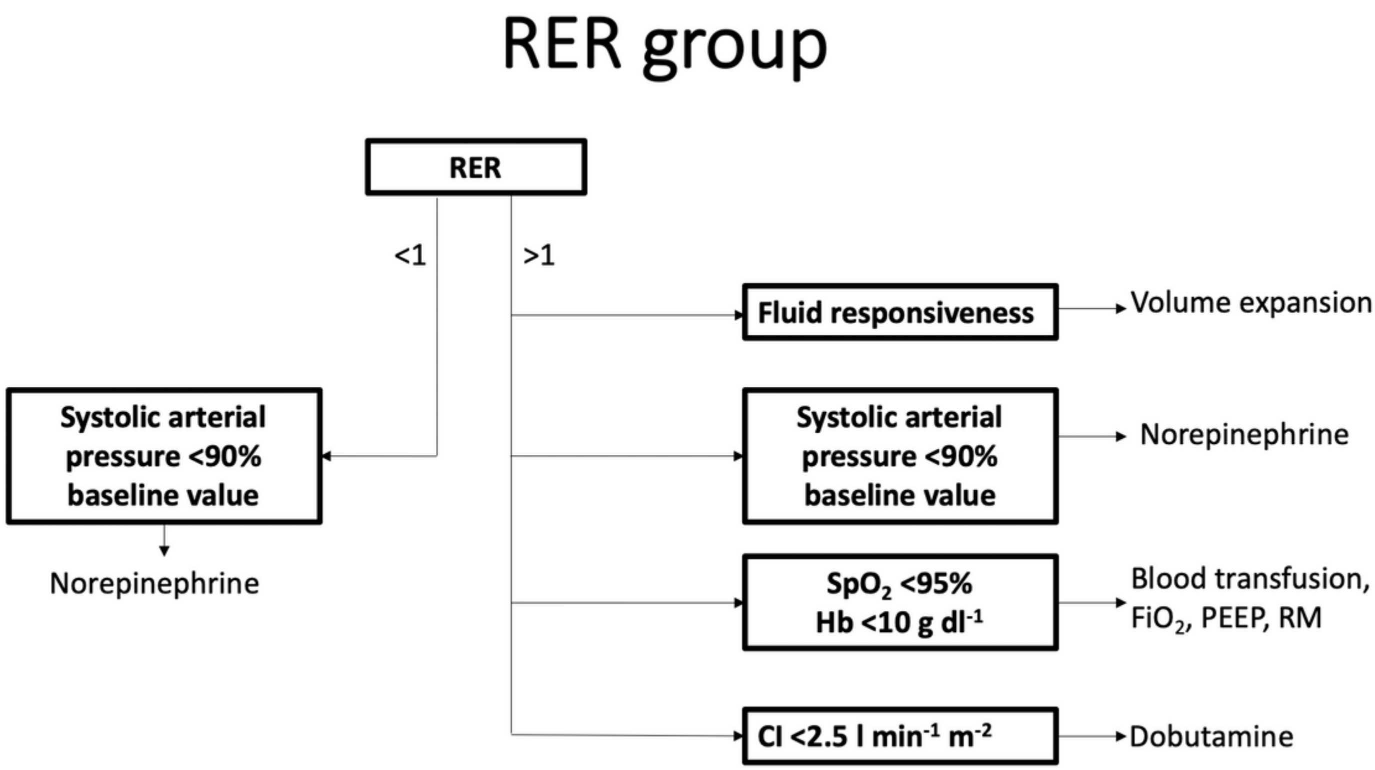

Figure 3

Algorithm for management in interventional group.