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# Sodium bicarbonate for the treatment of severe metabolic acidosis with moderate or severe acute kidney injury in the critically ill: protocol for a randomised clinical trial (BICARICU-2)

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## ABSTRACT

**Introduction** When both severe metabolic acidemia (pH equal or less than 7.20; PaCO2 equal or less than 45 mm Hg and bicarbonate concentration equal or less than of 20 mmol/L) and moderate-to-severe acute kidney injury are observed, day 28 mortality is approximately 55%–60%. A multiple centre randomised clinical trial (BICARICU-1) has suggested that sodium bicarbonate infusion titrated to maintain the pH equal or more than 7.30 is associated with a higher survival rate (secondary endpoint) in a prespecified stratum of patients with both severe metabolic acidemia and acute kidney injury patients. Whether sodium bicarbonate infusion may improve survival at day 90 (primary outcome) in these severe acute kidney injury patients is currently unknown.

**Methods and analysis** The sodium bicarbonate for the treatment of severe metabolic acidosis with moderate or severe acute kidney injury in the critically ill: a randomised clinical trial (BICARICU-2) trial is an investigator-initiated, multiple centre, stratified, parallel-group, unblinded trial with a computer-generated allocation sequence and an electronic system-based randomisation. After randomisation, the intervention group will receive 4.2% sodium bicarbonate infusion to target a plasma pH equal or more than 7.30 while the control group will not receive sodium bicarbonate. The primary outcome is the day 90 mortality. Main secondary outcomes are organ support dependences.

**Ethics and dissemination** The trial has been approved by the appropriate ethics committee (CPP Nord Ouest, Rouen, France, 25 April 2019, number: 19.03.15.72446). Informed consent is required. If sodium bicarbonate improves day 90 mortality, it will become part of the routine care.

**Trial registration number** NCT04010630.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Trial design: multiple centre randomised trial powered to conclude on the usefulness of sodium bicarbonate in critically ill patients with severe metabolic acidemia and acute kidney injury.
⇒ Sample size: largest trial ever conducted on sodium bicarbonate and metabolic acidemia in the critically ill population.
⇒ Trial pragmatism: population enriched trial comparing sodium bicarbonate (without the use of formula to calculate the amount of bicarbonate given) versus no sodium bicarbonate as per routine clinical use.
⇒ A double-blinded trial was not considered feasible because it would have necessitated masking the acid–base balance to clinicians in a population with severe acidemia on enrolment.

## INTRODUCTION

### Background and rationale

This manuscript was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[1] Severe metabolic acidemia is defined by the combination of pH ≤7.20, bicarbonataemia ≤25 mmol/L and PaCO2 ≤45 mm Hg. It is associated with a high rate of intensive care unit (ICU) mortality (up to 60%) in the critically ill population.[2 3] It accompanies a various spectrum of diseases and is secondary to different mechanisms.[4] Aside specific causes of metabolic acidosis such as ketoacidosis, exogenous acid poisoning etc, 50% of the critically ill patients who develop severe metabolic acidosis do present a combination of hyperlactataemia, and moderate-to-severe kidney injury.[3] Although the extensive review of the association between severe acidemia and organ injuries is beyond the scope of the present manuscript, severe metabolic acidemia has been associated decreased cardiac contractility and cardiac output, predisposition to cardiac arrhythmias, peripheral vasodilatation, hypotension, pulmonary hypertension.[4] Other deleterious effects such as impairment of the immune response and stimulation of inflammatory mediators have also been suggested.[4] On the other hand, increased tissue oxygen delivery

and increased blood flow to tissues secondary to vasodilation have also been reported.[4]

The treatment of metabolic acidemia using sodium bicarbonate is a matter of controversy. Experimental data and (most often single centre) observational studies have not suggested a benefit of sodium bicarbonate infusion in critically ill patients with acidemia while surveys did suggest that physicians largely prescribe sodium bicarbonate in their daily practice.[2 5–8] In a previous multiple centre randomised clinical trial, we found that in critically ill patients with severe metabolic acidemia (pH≤7.20) the infusion of sodium bicarbonate to target a pH equal or higher than 7.30 was not associated with a statistically significant difference in outcome (no difference in the primary endpoint which was the combination of organ failure at day 7 and mortality as well as the estimate of the probability of survival at day 28 between the control group and bicarbonate group: (46% (95% CI 40% to 54%) vs 55% (95% CI 49% to 63%); p=0.09 using the log rank test). However, in a prespecified stratum of patients with moderate-to-severe kidney injury, the infusion of sodium bicarbonate in comparison with no sodium bicarbonate infusion was associated with reduced rate of mortality from enrolment to day 28 between the control group and bicarbonate group: 63% (95% CI 52% to 72%) vs 46% (95% CI 35% to 55%); p=0.0283[3] as well as less renal replacement therapy requirement ((66/90 (73%) vs 47/92 (51%), absolute difference: −22.2 (95% CI −36 to −8.5), p=0.002). Although the BICARICU trial suggested a room for sodium bicarbonate in a subgroup of patients, this indication remains controversial and highly debated in the literature especially about the potential side effects of sodium bicarbonate infusion on homeostasis and the potential benefit of acidemia on cells metabolism and oxygenation.[9–12] Recognising the equipoise between sodium bicarbonate and no sodium bicarbonate in this subpopulation, we have chosen to conduct a further investigation into the use of sodium bicarbonate infusion in critically ill patients presenting with both severe acidemia and moderate-to-severe acute kidney injury (AKI).

## Objectives

### Primary objective

The main objective is to determine whether sodium bicarbonate infusion mitigates all causes day 90 mortality in critically ill patients with severe metabolic acidemia and moderate-to-severe acute kidney injury in comparison with no sodium bicarbonate infusion.

### Secondary objectives

The secondary objectives will be the comparison between the two groups (sodium bicarbonate group vs no sodium bicarbonate group) of the organ failure score (Sequential Organ Failure Assessment (SOFA) score at days 1, 2 and 7) and other secondary outcomes.

The main hypothesis is that sodium bicarbonate infusion will be associated with a decrease in day 90 mortality.

## Trial design

The BICARICU-2 trial is an investigator-initiated, multiple centre, stratified, parallel-group unblinded trial with a computer-generated allocation sequence and an electronic system-based randomisation. The intervention group will receive intravenous 4.2% sodium bicarbonate to target a plasma pH equal or greater than 7.30 while the control group will not receive intravenous sodium bicarbonate. We will randomly assigned patients by stratified randomisation with minimisation using a computer generated allocation sequence accessible from each centre through a secured dedicated website with stratification according to trial site, age with a cut-off of 65 years and enrolment pH (≤7.10 vs >7.10). This current study protocol has not been modified.

## CONSORT diagram

Figure 1 shows the CONSORT diagram of the BICARICU-2 trial.

## Eligibility criteria

### Inclusion criteria

An individual must fulfil all of the following criteria at the time of trial enrolment in order to be eligible:

- Aged from 18 years old.
- Admitted in the ICU where the BICARICU-2 trial takes place.
- Within 6 hours before enrolment, the patient MUST present on the same arterial blood gas (the last available before enrolment) the three following criteria
  - pH≤7.20.
  - Bicarbonataemia≤20 mmol/L
  - AND $PaCO_2$≤45 mm Hg.
- Moderate-to-severe acute kidney injury ('Kidney Disease Improving Global Outcome', group of 2 or 3).[13]
- Within 48 hours of ICU admission, a total SOFA≥4 or an arterial lactate concentration ≥2 mmol/L.
- Signed informed consent form. According to the French law, considering the severity of the illness, the fact that most of these patients would be unable to consent (need for sedation or potential delirium) and that their proxies might not be contactable at the time of inclusion, a deferred consent process for emergency situations was enabled. When deferred consent was used, written permission to pursue the research was obtained from the patient or proxy as soon as possible. If this consent was not obtained, the patient's data will not be used and they will be withdrawn from the trial.
- Subjects must be covered by public health insurance by the French law.

### Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included

- Pure respiratory acidosis (defined by pH≤7.20, $PaCO_2$≥50 mm Hg, bicarbonataemia equal or greater

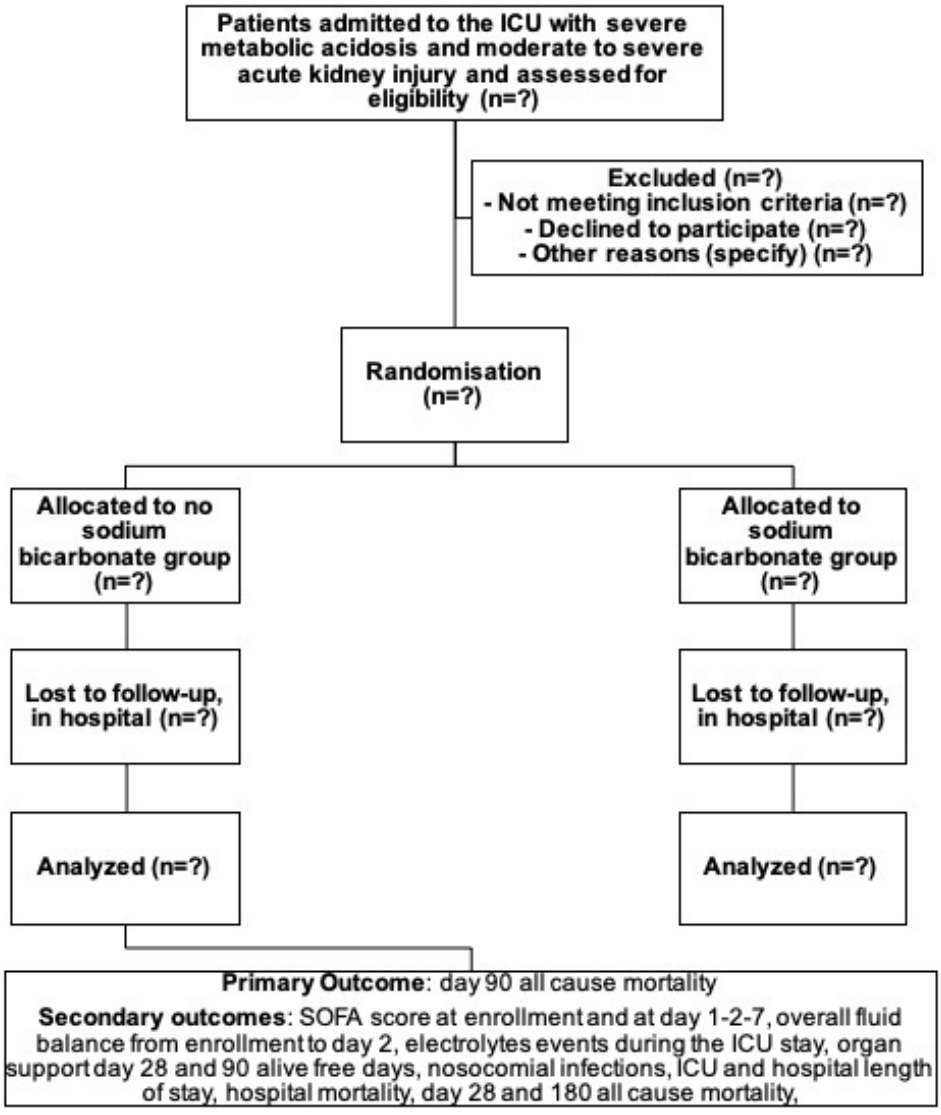


**Figure 1** CONSORT diagram of the BICARICU-2 trial. ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; CONSORT, Consolidated Standards of Reporting Trials.

than ($PaCO_2$−40)/10+24), digestive or urinary tract proven loss of fluid (equal or greater than 1500 mL/24 hours) with concomitant loss of sodium bicarbonate, stage IV or V chronic kidney disease, proven tubular acidosis, ketoacidosis, exogenous acids poisoning (aspirin, methanol,), $PaCO_2$≥45 mm Hg and spontaneous breathing, sodium bicarbonate infusion or renal replacement therapy within 24 hours prior to screening prior to screening or imminent in the next 6 hours.

- Pregnant or breastfeeding patient.
- Patient who is in a dependency or employment with the sponsor or the investigator.
- Patient who was enrolled in another study and who is in the exclusion period for any enrolment in the present trial
- Life expectancy less than 48 hours.
- Patients protected by law (Art.L 1121–5, 1121–6, 1121–8 of the French Health Code law register).

## Outcomes

### Primary outcome

The primary outcome is the day 90 all-cause mortality.

### Main secondary outcomes

The main secondary outcomes will be the following

1. Organ Failure assessed by the SOFA score (Time Frame: up to 7 days after enrolment).
2. Overall fluid balance (time frame: day 2).
3. Electrolytes adverse events during the ICU stay (time frame: ICU discharge or day 28).
4. Organ support (renal replacement therapy and mechanical ventilation) day 90 alive free days (time frame: day 90).
5. Hospital-acquired infections (time frame: ICU discharge or day 28).
6. Hospital length of stay (time frame: up to day 180).
7. ICU length of stay (time frame: up to day 90).
8. Day 28 all-cause mortality (time frame: day 28).

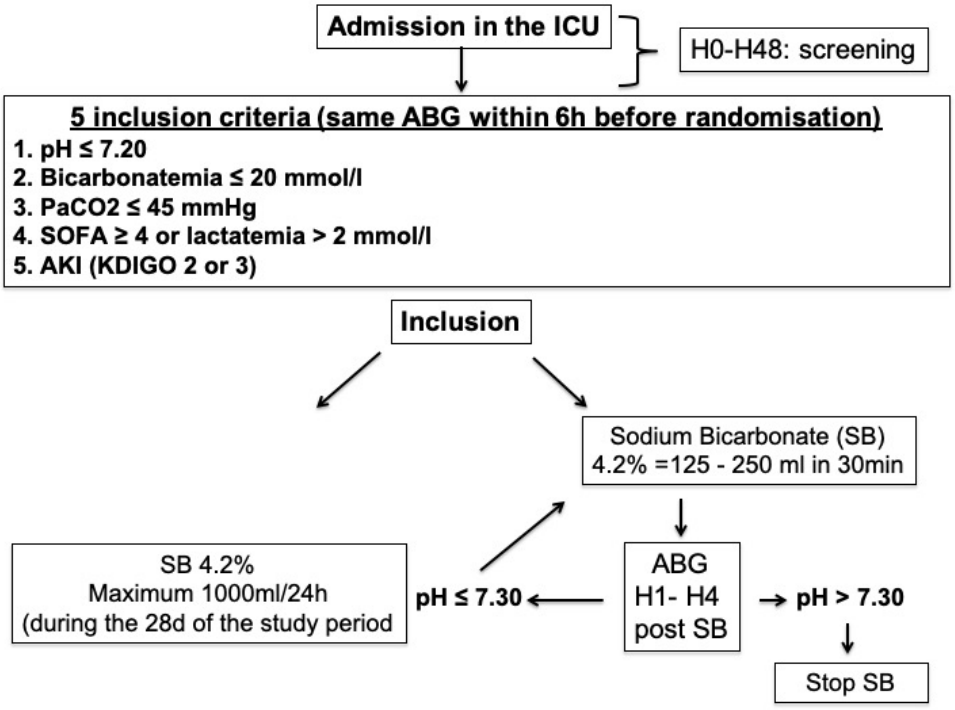


**Figure 2** Experimental design of the BICARICU-2 trial. The present trial design was similar than the previously published BICARICU-1 trial except for the inclusion criteria. ABG, arterial blood gas; AKI, acute kidney injury; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; SOFA, Sequential Organ Failure Assessment score.

9. Day 180 all-cause mortality (time frame: day 180).
10. Quality of Life of participant (time frame: up to day 180) only in the Montpellier Nimes centres with the centralised post-ICU outpatient clinic.
11. Functional autonomy of patient (time frame: up to day 180) only in the Montpellier Nimes centres with the centralised post-ICU outpatient clinic.

### Main safety outcomes

The main safety outcomes will be the incidence, relatedness and severity of treatment-emergent adverse events evaluated at each visit until the end of the trial. According to the BICARICU-2 trial,[3] adverse events will be defined as

- Non-serious: hypernatraemia ≥145 mmol/L without associated neurological disorders, hypokalaemia <3.2 mmol/L without ECG signs, ionised hypocalcaemia <0.9 mmol/L without ECG signs, alkalaemia (pH≥7.45).
- Serious: acute oedema of the lung, severe hypokalaemia with repolarisation disorders and/or cardiac arrhythmias, severe hypocalcaemia with repolarisation disorders and/or cardiac arrhythmias and/or ECG signs of intolerance and cardiopulmonary oedema.

## Interventions

Patients eligible for inclusion will be randomly assigned to the experimental group (bicarbonate group) or to the control group (no bicarbonate) (figure 2).

### Experimental (sodium bicarbonate) group

Patients randomly assigned to bicarbonate group (sodium bicarbonate 4.2%) will received trial dedicated intravenous 4.2% sodium bicarbonate titrated from 125 mL to 250 mL in 30 min at physician's discretion to target a pH equal or above 7.30. Bicarbonate infusion will be repeated at a maximal volume of 1000 mL per 24 hours. Arterial blood gases will be repeated from 3 to 6 times during the first 24 hours at physician's discretion.

Bicarbonate infusion recommendations will be as follow: a central line is strongly recommended, infusion flow should be performed at 125–250 mL in 30 min with no intravenous push, careful surveillance of metabolic alkalosis, cardiogenic pulmonary oedema, kalaemia, natraemia and calcaemia. Repeated arterial blood gases will be suggested to monitor these critically ill patients and physicians will be informed of the potential side effects of sodium bicarbonate infusion (hypokalaemia, hypocalcaemia, alkalaemia, hypernatraemia, fluid overload).

### Control group (no sodium bicarbonate group)

In the control group, patients will not receive any sodium bicarbonate infusion.

There is currently no fluid solution that is associated with no impact of acid–base equilibrium and we can not blind the clinicians for the pH and bicarbonataemia trend over the ICU course of these critically ill patients. We have, therefore, as in the BICARICU-1 trial[3] chose to compare sodium bicarbonate versus no sodium bicarbonate infusion.

### Both experimental and control groups

In both groups of patients, criteria will be applied to suggest the need of invasive mechanical ventilation and the renal replacement therapy as follow:

- Invasive mechanical ventilation: respiratory failure with one of the following criteria: respiratory arrest, circulatory arrest, gasps, coma with Glasgow Coma Scale of 8 or below, copious secretions with incapacity to clear the secretions, bradycardia below 50/min with loss of consciousness, circulatory shock needing high dose of vasopressors. Invasive mechanical ventilation will also be suggested in case of respiratory failure with at least two of the following criteria: respiratory acidosis (arterial pH≤7.35 together with PaCO2≥45 mm Hg); arterial O2 saturation by pulse oximetry of less than 90% or PaO2 lower than 60 mm Hg at FiO2 of 0.5 or more; respiratory frequency greater than 35 breaths per min; diminished consciousness, agitation or diaphoresis and clinical signs suggestive of respiratory muscle fatigue, increased work of breathing or both such as use of respiratory accessory muscles, paradoxical motion of the abdomen or retraction of intercostal spaces. Invasive mechanical ventilation will be analysed as a secondary endpoint.
- Renal replacement therapy: on ICU admission and at any time after enrolment, renal-replacement therapy will be strongly recommended when facing kalaemia above 6.5 mmol/L with ECG signs and/or cardiogenic pulmonary oedema with no urine output and PaO2/FiO2<200 with FiO2>50% and PEEP>5 cmH2O. Renal-replacement therapy will be suggested when facing at least two criteria among the following and after 24 hours of enrolment: urine output less than 0.3 mL/kg/24 hours, a pH≤7.20 despite resuscitation or kalaemia above 6.5 mmol/L. Renal replacement therapy will be analysed as a secondary endpoint. Although pH was one of the criteria used in the recent trials[3 14 15] to trigger the initiation of renal replacement therapy, the BICARICU-1 trial suggests that sodium bicarbonate may delay or even avoid in some patients the need for renal replacement therapy. Furthermore, even if acidemia is one of the reason to start renal replacement therapy in the critically ill according to a recent survey,[16] the threshold and the timing to start the therapy is currently unknown. This is the reason why we will recommend in the BICARICU-2 trial, as for BICARICU-1 trial, to start the therapy in case of a persistent acidemia despite 24 hours of resuscitation.

### Participant timeline

The participant timeline is described in table 1.

### Sample size

Based on the BICARICU-1 trial where day 90 mortality was 81% in the control group and 64% in the bicarbonate group (post hoc analysis of BICARICU-1 trial,[17]) in the population of interest for the BICARICU-2 trial (severe metabolic acidosis and severe acute kidney injury in the critically ill patients), we calculated that a total of 588 patients would be needed for 80% power to show an absolute between-groups difference of 10% in the primary outcome (day 90 all-cause mortality) at a two-sided alpha level of 0.05 (overall p value for the trial), assuming that the administration of bicarbonate would be associated with a day 90 mortality of 70% vs 80% in the control group. Assuming less than 8% non-analyzable patients (lost to follow-up or consent withdrawal; the same rate as in the BICARICU-1 trial), we plan to enrol 640 patients. Two interim analyses are planned. Assuming the overall p value for the trial is 0.05, p value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary).

### Recruitment

Patients are expected to be included during a 3-year inclusion period starting November 2019. Among the 35 participants centre, each one would include one patient per month during the 36 months trial period.

March 2019–October 2019: Protocol, approvals from ethics committee and trial tools development (case report form, randomisation system).

March 12 2020: Ethics committee authorisation to enrol more centres in the trial.

June 9 2021: Ethics committee authorisation to enrol more centres in the trial due to an unexpected decrease in enrolment rates during the pandemic.

November 2019 to ongoing: Inclusion of patients.

## METHODS: ASSIGNMENT OF INTERVENTIONS

### Allocation and sequence generation

Randomisation will be managed by the clinical research unit of Montpellier University Hospital with Capture System software (Ennov Clinical, randomisation module). The randomisation will be centralised and available online. It will be stratified on centre, age and pH balanced with a 1:1 ratio and blocks of variable sizes.

### Blinding

Given the nature of the solutions and their impact on acid–base equilibrium, a blinded design is not possible for the investigator and associate investigator. The methodologist will be blinded to the group.

## METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

### Data collection and management

- Data will be collected and recorded on electronic case report forms by trained local research coordinators or physicians. Sociodemographic data (age, sex, weight, height, reason for ICU admission, medical history, main cause of acute kidney injury, SAPSII score) will be collected on enrolment.

Table 1 Participant timeline

| | Screening/baseline | | Final visit |
|---|---|---|---|
| Item | V 1 | V 2 | V 3 |
| Date | Day 0 | Days 190 | Day 180 |
| Clinical evaluation | X | | |
| Informed consent | X | X* | |
| Randomisation | X | | |
| Medical history | X | | |
| Demography | X | | |
| Physical examination | X | X | |
| Vital signs† | X | X | |
| Routine laboratory testing‡ | X | X | |
| Experimental treatment | x | x | |
| Endpoints evaluation§ | | x | X |
| AE recording | | X¶ | |

*Informed consent: consent from the patient can be obtained at enrolment but might be confirmed (after or emergency enrolment if the patient cannot consent because of sedation) later during the ICU course and up to the ICU discharge day.
†Vital signs include temperature, heart rate and arterial blood pressure.
‡Routine laboratory testing (blood): haemoglobin, haematocrit, RCC, WCC, PC; INR, PTT, electrolytes, creatinine, ALT, AST, AP, LDH, CRP, arterial blood gases, lactate, albumin.
§Status (alive vs dead) will be collected daily from enrolment to day 90 (main outcome) and at day 180. SOFA score will be collected at enrolment at day 1, day 2 and day 7; electrolytes and fluid balance will be collected at enrolment, day 1, day 2. Electrolytes AEs and nosocomial infections will be collected during the ICU stay with a censored date at day 28. Organ support and ICU and Hospital length of stay will be collected during the ICU stay with a censored date at day 90. Quality of Llife (EQ5D) and autonomy score (Functional Independence Measure score) will be collected at Dday 90 and Dday 180 solely at the Montpellier - Nimes site.
¶Until day 28.
**
AE, adverse event; ALT, Alanine transaminase; AP, Alkaline Phosphatase; AST, Aspartate transaminase; CRP, C reactive protein; EQ5D, European Quality of Life Five Dimension; ICU, intensive care unit; INR, International Normalised Ratio; LDH, Lactate Deshydrogenase; PC, Platelets Count; PTT, Partial thromboplastin time; RCC, red cell count; SOFA, Sequential Organ Failure Assessment; WCC, white cell count.

The primary outcome (day 90 all-causes mortality) will be collected at each trial site. The following secondary outcomes will be collected

- SOFA score[18] at enrolment and at 1 day, 2 days and 7 days after enrolment.
- Overall fluid balance and solutions intake from enrolment to day 2.
- Electrolytes and acid–base status from enrolment to H48.
- Organ support therapies (renal replacement therapy, mechanical ventilation, vasopressors) day 28 alive free days.
- Day 90 renal replacement therapy dependency.
- Nosocomial infections (pneumonia, bacteraemia, urinary tract infection, central line associated blood stream infections) during the ICU stay.
- ICU and hospital length of stay.
- Hospital mortality, day 28 and day 180 all-cause mortality.

Day 90 and day 180 quality of life and autonomy score (ancillary study only in Montpellier Nimes teaching centres with the centralised post-ICU outpatient clinic).

- Presence of treatment limitations during the ICU stay.

## Patients and the public involvement

Patients and the public were not involved in any way.

## Data and safety monitoring board and interim analysis

An independent data and safety monitoring board (DSMB) will be appointed to oversee the conduct of the trial and review one interim analysis. The DSMB will be composed of two academic intensivists experienced in the conduct of clinical trials. The DSMB will conduct a double interim analysis for efficacy and safety, after enrolment of 200 patients and 400 patients. The DSMB will be blinded to the treatment arm. The interim analysis will be planned for early stopping of the trial owning to safety or efficiency on the primary outcome after the first 200 and 400 patients included assuming the overall p value for the trial is 0.05, p value threshold is 0.001 for the two interim analyses and 0.05 for the final analysis (Haybittle-Peto boundary). Although no prespecified rules was implemented in the first version of the protocol, we implemented at the DSMB request the following stopping rules for futility after the first interim analysis (6 October 2021, MSA CPP No 03: the futility is defined as an absolute between-groups difference of 4% or less in the primary outcome (this

threshold for the between-groups difference of 4% is associated with a final statistical power arrowed 20%).

## Statistical methods

### Statistical analysis

A predefined statistical analysis plan will be followed. The statistical analysis will incorporate all the elements required by the CONSORT statement for pharmacological interventions. Statistical analysis will be performed in an intention to treat population, including all the randomised patients except patients who withdraw their consent or do not meet the inclusion criteria. A per-protocol analysis will be performed among the patients included in the intention-to-reat analysis. The per-protocol analysis will take into account if sodium bicarbonate was eventually administered or not in enrolled patients.

All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, V.9.3; SAS Institute and R, V.3.5.0). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

## Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described, using frequencies and percentage for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables according to their distribution.

## Primary analysis

An adjusted $\chi^2$ test will be done to compare day 90 mortality proportion between groups. We will perform a multiple logistic regression for the primary outcome. The survival time will be described by means of Kaplan-Meier method and compared with a log-rank test. A Cox proportional-hazards model will be used to calculate HRs for death. For this analysis, data from all patients will be censored at the time of death or at day 90. Logistic and Cox regression models will be adjusted on relevant baseline covariates. Covariates will be defined as binary variables and continuous variables dichotomised according to their median tested in the model, and will be selected in a backward selection procedure if $p<0.15$ in the univariate analysis and then presented as adjusted ORs or HRs with 95% CIs. For multiple comparisons in each prespecified stratum, a Holm-Bonferroni method will be done to compute an adjusted p value. A mixed regression model will be used to model repeated measures. Interactions between variables and time will be tested. We will also perform all the analyses described above among prespecified strata of the randomisation. Tests for all outcomes will be two sided.

## Secondary analyses

We will conduct the following prespecified secondary analyses:

### Secondary and exploratory outcomes

We will perform unadjusted, intention-to-treat analyses comparing patients in the sodium bicarbonate group to patients in the no sodium bicarbonate group with regard to each of the prespecified secondary and exploratory outcomes.

Continuous outcomes will be compared with the Mann-Whitney rank-sum test and categorical variables with the $\chi^2$ test. For repeated data, a mixed linear model will be used, including the subject as a random variable.

### Per-protocol analysis

The per-protocol analysis will exclude patients with major protocol violations and will compare patients that did receive sodium bicarbonate group with patients that did not receive sodium bicarbonate group (regardless of group assignment).

### Effect modification (subgroup analyses)

We will examine whether prespecified baseline variables modify the effect of study group on the primary outcome. We will evaluate for effect modification by fitting a logistic regression model for the primary outcome. Independent variables will include study group assignment. Subgroups derived from categorical variables will be displayed as a forest plot. Continuous variables will be analysed using restricted cubic splines with 3–5 knots and preferentially displayed as continuous variables using a locally weighted regression or partial effects plots. If the presentation of data requires it, dichotomisation of continuous variables for inclusion in a forest plot will be performed. Prespecified subgroups that may modify the effect of infusing sodium bicarbonate include: pH≤7.10, pH (as a continuous variable), age <65 yo, presence of sepsis, SOFA score on enrolment (median score).

## Missing data

Based on the prior trial performed in similar settings, we anticipate less than 5% missing data for the primary outcome. Missing data will not be imputed. Analyses will be performed on the complete cases. We will indicate in each table the number of observed data.

# METHODS: MONITORING

## Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICUs will attend formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the trial protocol and collecting the trial data, with blinded assessment.

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in

case of major serious adverse events suspected to be associated with the technique of intubation used.

### Auditing

An independent DSMB, composed of three experts will monitor the safety of the trial.

### Ethics and dissemination

#### Research ethics approval

This research involving humans will be conducted in compliance with the French law 'Loi no 2012–300 du 5 mars 2012 relative aux recherches impliquant la personne humaine (Loi Jardé'), 'Loi No 78-17 du 6 janvier 1978 modifiée relative à l'Informatique, aux fichiers et aux Libertés'). This trial will be conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation. The trial has been approved by the ethics committee 'Comité de Protection des Personnes Nord Ouest 1 (ref 19.03.15.72446)'. The BICARICU-2 trial is conducted in accordance with the Declaration of Helsinki and was registered at http://www.clinicaltrials.gov (NCT04010630) 8 July 2019. The first patient was enrolled on 6 October 2019.

#### Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki (online supplemental appendix 1). If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of underlying disease. These patients will be included after written informed consent is provided by next of kin or a vital emergency procedure (investigator signature) if next of kin is not present. When available, after recovery, patients will be retrospectively asked for written consent to continue the trial.

#### Confidentiality

Data will be handled according to the French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymised and kept for 15 years.

#### Declaration of interest

The trial is an investigator-initiated trial. Trial promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

#### Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. All investigators will have access to the final data set. Participant-level data sets will be made accessible on a controlled access basis.

## DISCUSSION

The BICARICU-2 trial will be the first randomised clinical trial to investigate whether sodium bicarbonate infusion is associated with day 90 mortality in critically ill patients with both severe acidemia (pH≤7.20) and moderate-to-severe AKI. We will also explore whether sodium bicarbonate infusion, targeted to maintain an arterial pH equal or greater than 7.30, is associated with less organ support dependence, a shorter length of stay in the ICU and in the hospital.

Whether sodium bicarbonate is beneficial in that subset of patients is a matter of debate in 2023. Since the publication of the BICARICU-1 trial, a few observational studies but no randomised clinical trial have been published. Interestingly, these studies enrolled patients with moderate acidemia (pH≤7.30) instead of severe acidemia (pH≤7.20).

In 18 ICUs in Australia, Japan and Taiwan, 1292 consecutive critically ill adult patients with early and moderate metabolic acidosis (pH≤7.3 and a Base Excess ≤−4 mEq/L, within 24 hours of ICU admission) were evaluated. Among them, 233 (18%) received sodium bicarbonate. The patients who did receive sodium bicarbonate were sicker than the ones who did not. After adjusting for confounders, sodium bicarbonate was associated with higher mean arterial pressure at 6 hours among the patients with vasopressors dependency but not with mortality.[19] In a single centre retrospective study using the open access MIMIC-3 database, 869 patients older than 60 years old with sepsis and moderate metabolic acidosis (pH≤7.3 and bicarbonataemia less than 20 mmol/L) were evaluated according to whether they received sodium bicarbonate or not within 48 hours after the ICU admission.[12] Both ICU and hospital mortality were significantly reduced in the subgroup of patients with moderate metabolic acidemia (7.2<pH<7.3) treated with sodium bicarbonate. Using the same MIMIC-3 database and moderate acidemia (pH<7.30), Wang *et al* suggested that sodium bicarbonate was not associated with survival and that sodium bicarbonate might be associated with worsening organ failure score in a subset of patients with unchanged or deteriorating haemodynamics before sodium bicarbonate infusion.[20]

One strength of the BICARICU-2 trial is the planned enrolment of 640 patients with both severe acidemia (pH≤7.20) and moderate-to-severe acute kidney injury. Contrary to the observational studies that enrolled moderately ill patients with no inclusion criteria about kidney function, we will focus on a very high mortality group of patients. The BICARICU-2 trial is not blinded because first there is no solution with no effect on the acid–base balance and second because it is unethical to blind the caregivers to the pH trend during the first hours of the ICU stay. Blinding them for pH would obligate them to navigate without this crucial information. On the other hand, making the pH available in both groups would

per se give them the information about the group of randomisation.

We believe that, if sodium bicarbonate, a medication worldwide available for almost no additional cost in most of the countries around the globe, is associated with a better outcome it would change the way of treating these critically ill patients.

## Trial status

The trial has actively enrolled since November 2019.

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**Contributors** BJ drafted the manuscript. BJ designed the trial together with SJ. HH and NM wrote the statistical analysis plan and estimated the sample size. All authors revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

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**Competing interests** SJ reports receiving consulting fees from Drager, Medtronic, Mindray, Baxter, Fisher & Paykel and Fresenius-Xenios. No potential conflict of interest relevant to this article was reported for other authors.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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INFORMATION SHEET FOR PARTICIPANTS IN THE BICAR ICU 2 STUDY

Study Title: Adjuvant Treatment of Severe Metabolic and/or Mixed Acidosis with Moderate to Severe Acute Renal Failure using Sodium Bicarbonate: A Prospective Multicenter Randomized Controlled Study

National Reference: 2019-000671-16 Project Coordinator: Dr. Boris JUNG (University Hospital of Montpellier)

Principal Investigator at your institution:

……

Dear Sir/Madam,

Your doctor has proposed your participation in a clinical research study currently taking place in our department entitled: Adjuvant Treatment of Severe Metabolic and/or Mixed Acidosis with Moderate to Severe Acute Renal Failure using Sodium Bicarbonate: A Prospective Multicenter Randomized Controlled Study, promoted by the University Hospital of Montpellier.

We kindly invite you to carefully read this information sheet, which aims to address any questions you may have before making your decision to participate. After reviewing the information sheet, you will have a period of time to consider before submitting the corresponding signed consent form.

Your participation is entirely voluntary. If you do not wish to participate in this research, you will continue to receive the best possible medical care in accordance with current knowledge.

1. Why this research? You have a disease that poses a short-term life-threatening risk. Among the consequences of your illness, there is blood acidification (known as acidemia) and sudden kidney failure (known as acute renal failure). Treatment that corrects this acidification through infusion (using sodium bicarbonate treatment) could potentially improve your health, but this remains uncertain at present. We aim to evaluate this treatment through this study conducted in multiple centers in France.
2. What is the research objective? The objective of the research is to determine if adjuvant treatment (additional treatment) using sodium bicarbonate infusion allows for a faster treatment of severe acidosis in patients with moderate to severe renal failure admitted to the intensive care unit. "Severe acidosis" is characterized by a decrease in blood pH, making it acidic. The causes of this acidity are multiple in intensive care (infections, etc.), with acidosis reflecting the severity of the disease.
3. What is the methodology? This is a therapeutic trial that will be conducted in over thirty healthcare institutions in France, where 640 patients will be recruited over a period of 5 years. As part of this project, a computerized randomization will be

performed to determine whether or not you will receive sodium bicarbonate (adjuvant) in addition to the standard treatment for your illness. Two groups of patients will be formed as a result. This procedure is commonly used in clinical research to scientifically address the study's objectives. If you receive sodium bicarbonate, it will be administered by infusion (through an existing catheter for your monitoring) at a dose of 125 ml to 250 ml of 4.2% sodium bicarbonate, with a maximum of 1000 ml to correct the pH with a target of 7.30. The quantity administered and the frequency of administrations will be adjusted according to your pH during your stay in the intensive care unit. If you do not receive sodium bicarbonate, you will be treated according to good practice recommendations. Therefore, the management of your illness will be the same regardless of whether or not you receive sodium bicarbonate."

**What will be your care, treatment schedule, and medical follow-up?**

If you agree to participate in the study and meet all the required conditions, after signing the informed consent, you will be monitored during your stay in the intensive care unit. You will receive either the adjuvant treatment with sodium bicarbonate or the specific therapeutic care planned by the doctor. Your health status and biological parameters will be monitored throughout your stay. After your discharge, you will be contacted by phone at 3 months and 6 months to check on your progress. The table below summarizes the care planned by the study:

| **Date** | Day 0: Admission to the intensive care unit (ICU) | Day 0: Admission to the intensive care unit (ICU) | Day 0: Admission to the intensive care unit (ICU) |
|---|---|---|---|
| Verification of inclusion criteria for the study | **X*** | | |
| Information about the study and obtaining your informed consent | **X*** | | |
| Collection of your medical history | **X** | | |
| Clinical examinations by the physician | **X** | **X** | |

| | | | |
|---|---|---|---|
| Monitoring of your biological parameters (blood tests) | **X** | **X** | |
| Randomization (drawing lots) | **X*** | | |
| Treatment with sodium bicarbonate for the treated group | **X*** | **X*** | |
| Follow-up of your health condition and acidosis | | **X** | |
| Quality of life questionnaires for patients followed in Montpellier and Nimes (approximately 10 minutes duration) | | | **X*** |
| Outcome | | | **X*** |

*study-specific

**What are the expected benefits?**

For patients in the treated group, the potential benefit you could expect from participating in this study is a faster improvement of acidosis, meaning an increase in blood pH, which could help your organs (heart, kidneys, lungs) function better and more quickly. Conversely, if you do not receive sodium bicarbonate treatment, the correction of blood pH will be slower. However, in any case, you will receive appropriate therapeutic care tailored to the causes of your acidosis and determined by your doctor outside of the research."

**What are the foreseeable risks?**

Sodium bicarbonate is an authorized and commercially available medication indicated for correcting metabolic acidosis. In the context of the study, possible adverse effects related to the infusion of sodium bicarbonate are mainly disturbances in certain ions or particles such as sodium, potassium, and calcium in the blood. These imbalances are common in patients in the intensive care unit regardless of their treatment, but they are exceptionally severe

because blood tests are performed several times a day as part of routine monitoring to detect and manage them. Adjustments in potassium and calcium intake, as well as a decrease in sodium intake, can easily be implemented by the medical intensive care team. In very rare cases, the pH can increase too much (over-correction of acidity), leading to a condition known as "rebound alkalosis," which can also be easily detected through the multiple blood tests performed daily on intensive care unit patients. Furthermore, the administration of sodium with sodium bicarbonate infusion may represent an excess of sodium for patients with severe heart failure. However, patients in the intensive care unit are constantly monitored by a nurse, and the medical team is trained to detect and manage the very rare decompensations of heart failure during sodium bicarbonate treatment.
The non-administration of adjuvant treatment with sodium bicarbonate also exposes patients to the risks of slower correction of blood acidity, particularly the risks of cardiac rhythm disorders, decreased cardiac pumping strength, breathing difficulties, or neurological disorders such as coma. Prolonged significant acidity in the blood poses a life-threatening risk, although it is not yet known whether this is due to the acidity itself or rather the underlying disease that makes the blood more acidic.
These described side effects are not systematic and are generally well-tolerated.

**What will be the duration of your participation?**

If you agree to participate in this study, your participation will last for the duration of your stay in the intensive care unit. You will then be contacted by phone at 3 months and 6 months.

**What are the procedures and justification for sample collection?**

Blood samples from intensive care unit patients with abnormal blood acidity are necessary to adjust the treatment and monitor patients' progress. Significant blood acidity is an important sign that the disease is severe. No additional blood samples beyond those absolutely necessary for your monitoring as part of your care will be taken.

**What are the potential medical alternatives?**

Blood acidity spontaneously corrects itself with specific disease-specific treatment (e.g., antibiotics for infections), and it indicates recovery. The objective of this study is to determine whether accelerating the correction of acidity improves the success of specific treatment and speeds up recovery. The alternative to the study treatment (sodium bicarbonate) in France is the absence of treatment because there are no other available medications. However, if the

acidity remains severe, it may require the temporary implementation of renal dialysis, which is a machine that replaces the natural function of toxin and acidity elimination performed by your kidneys.

**What are your rights?**

Your doctor must provide you with all the necessary explanations regarding this research. If you wish to withdraw from the study at any time, for any reason, you will continue to receive medical follow-up, and it will not affect your future monitoring. According to regulations, you must have social security coverage to participate in research involving human subjects.

In accordance with Article L.1111-6 of the Public Health Code, you have the right to designate a trusted person who can be a family member, a close relative, or your treating physician. This person will be consulted in case you are unable to express your will and receive the necessary information for this purpose.

"Your will is important. The testimony of your designated trusted person takes precedence over any other testimony. This designation must be made in writing and co-signed by the designated person. It can be revised or revoked at any time.
If you wish, your trusted person can accompany you in your procedures and attend medical interviews to assist you in your decisions.

In the context of the research in which the University Hospital of Montpellier proposes your participation, computer processing of your personal data will be carried out to analyze the research results in relation to the presented objective.
The controller of this processing is the University Hospital of Montpellier.

The principal investigator of the study and any other study personnel bound by professional secrecy and under the responsibility of the attending physician will collect medical data concerning you. These pieces of information, referred to as "Personal Information," will be recorded on the observation forms, called observation notebooks, provided by the sponsor. Only information strictly necessary for processing and the purpose of the research will be collected in a secure database, and will be retained by the sponsor for 25 years after the research ends.
To ensure the confidentiality of your personal information, neither your name nor any other information that would directly identify you will be entered in the observation notebook or in

any other file that the study investigator will provide to the research sponsor or to individuals or companies acting on its behalf, in France or abroad.

These data will be identified by a code (inclusion number and initials). The code will be used by the study investigator to identify you if necessary.
Under conditions ensuring their confidentiality, this data may also be transmitted to French health authorities.
In accordance with the provisions of the French Data Protection Act (Law No. 78-17 of January 6, 1978, relating to data processing, files, and individual liberties, as amended by Law No. 2018-493 of June 20, 2018, relating to personal data protection) and the General Data Protection Regulation (EU Regulation 2016/679), you have the right to access, rectify, erase, or restrict the information collected about you in the context of this processing.
In certain cases, you can also refuse the collection of your data and object to certain types of data processing. You also have the right to object to the transmission of data covered by professional secrecy that may be used in the context of this research and to be processed.
You can also directly access, or through the physician of your choice, all of your medical data in accordance with the provisions of Article L1111-7 of the French Public Health Code.

You may withdraw your consent to the collection of your data at any time in the context of this processing. In this case, in accordance with Article L.1122-1-1 of the French Public Health Code, the data concerning you that have been collected prior to your withdrawal of consent may not be deleted and may continue to be processed in accordance with the research provisions.

Finally, you can request that the personal information collected be provided to you or to a third party in a digital format (right to data portability).

The aforementioned rights can be exercised with the physician who is following you in the context of the research and who knows your identity.

If you have any other questions regarding the collection, use of your personal information, or the associated rights, you can contact the Data Protection Officer of the University Hospital of Montpellier (email: dpo@chu-montpellier.fr) or the principal investigator of the study.

If, despite the measures put in place by the sponsor, you believe that your rights are not being respected, you can file a complaint with the competent data protection supervisory authority in France, the National Commission for Data Protection and Liberties (CNIL).

If the data controller wishes to carry out further processing of personal data concerning you for a purpose other than that for which your personal data were collected, you will be informed in advance of this other purpose, the duration of the retention of your data, and any other relevant information to ensure fair and transparent processing.

In accordance with Law No. 2012-300 of March 5, 2012, regarding research involving human subjects:

This research has obtained a favorable opinion from the Committee for the Protection of Persons of Nord Ouest 1 and the authorization of the National Agency for the Safety of Medicines and Health Products (ANSM).
The sponsor of this research has taken out civil liability insurance (contract number 166244) with the Société Hospitalière d'Assurances Mutuelles located at 18 rue Edouard Rochet, 69372 LYON CEDEX 08, France - 04 72 75 50 25).
Individuals who have suffered harm following participation in research involving human subjects may assert their rights with the regional commissions for conciliation and compensation for medical accidents.
When this research is completed, you will be personally informed of the overall results by your physician as soon as they become available, if you so desire.
After reading this information sheet, do not hesitate to ask your physician any questions you may have. After a period of reflection, if you agree to participate in this research, you must complete and sign the consent form. A copy of the complete document will be provided to you."

**CONSENT FORM FOR PATIENTS PARTICIPATING IN RESEARCH**
**BICAR ICU 2**

**Study Title: Adjuvant Treatment of Severe Metabolic and/or Mixed Acidosis with Moderate to Severe Acute Renal Failure using Sodium Bicarbonate: A Prospective Multicenter Randomized Controlled Study**

**National Reference: 2019-000671-16**
**Project Coordinator: Dr. Boris JUNG (University Hospital of Montpellier)**

Investigating Physician at your institution:
……

I, the undersigned (full name), certify that I have read and understood the information provided to me.
I had the opportunity to ask any questions I wanted to Dr./Prof. (name) who explained to me the nature, objectives, potential risks, and constraints associated with my participation in this research.
I am aware that I have the option to withdraw from this research at any time without having to justify my decision, and I will make every effort to inform the physician overseeing my participation. This will not affect the quality of subsequent care.
I have been assured that decisions regarding my health will be made at any time in accordance with the current state of medical knowledge.
I understand that this research has received favorable opinion from the Ethics Committee (Comité de Protection des Personnes) Nord Ouest 1, authorization from the ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé), and compliance with the General Data Protection Regulation.
The research sponsor (University Hospital of Montpellier - 191, avenue du G GIRAUD 34295 Montpellier Cedex 5) has obtained liability insurance coverage for potential harm from the Société Hospitalière d'Assurances Mutuelles (contract number 166244), located at 18 rue Edouard Rochet, 69372 LYON CEDEX 08, France – 04 72 75 50 25).
I accept that individuals collaborating on this research or appointed by the sponsor, as well as potentially the representative of Health Authorities, may have access to information with the utmost respect for confidentiality.
I agree that the data collected during this research may be subject to computer processing under the responsibility of the sponsor.

I have taken note that, in accordance with the provisions of the law relating to information technology, files, and freedoms, I have the right to access, rectify, limit the processing of my data, and lodge a complaint with the National Commission on Informatics and Liberties (CNIL): https://www.cnil.fr/. I also have the right to object to the transmission of data covered by professional secrecy that may be used in the context of this research and processed. Lastly, I have the right to withdraw my consent at any time. These rights can be exercised with the physician overseeing my participation in this research, who is aware of my identity. My consent in no way relieves the investigator and the research sponsor of their responsibilities towards me. I retain all rights guaranteed by law.
The overall results of the research will be directly communicated to me if I wish, in accordance with the law of March 4, 2002, concerning patients' rights and the quality of the healthcare system.

Having had sufficient time for reflection before making my decision, I freely and voluntarily agree to participate in the BICAR ICU 2 research.
At any time, I may request additional information from the physician who invited me to participate in this research.

Date: ……..

Date: ……..
Patient's Signature: Physician's Signature: