Full title of the research: **The impact of systemic pH on cardiac function and clinical outcome in the critically ill patient.**

IRAS Project ID: **227870**

Observational Protocol Template: KCH/KCL Sponsored Studies

Guidance

This protocol template is for use by **KCH/KCL investigators to submit studies for KCH or KCL Sponsorship** via the KCH Research & Innovation Office.

This template is **not applicable** for all studies:

- deemed to be Clinical Studies of Investigational Medicinal Products (CTIMP)
- involving new Devices or Devices being used for a new purpose

This template has been developed to include all relevant regulatory, ethics and local policy requirements. The template contains all sections recommended by the Health Research Authority (HRA) for regulatory review by the HRA and the Research Ethics Committees.

Investigators may use other templates, but must ensure the sufficient level of detail is presented. Investigators wishing to do so are encouraged to read through this template. Text marked in **black** must be inserted into these protocols.

The R&I Office will review each protocol submitted to ensure key sections and details are included before Sponsorship is formally agreed.

Instructions for use

Not all sections will be relevant for all studies. Each section can be modified or deleted as applicable to your type of study.

Instructions and explanatory text are indicated in **red** and should be removed or replaced in your protocol with the appropriate text.

Full title of the research: **The impact of systemic pH on cardiac function and clinical outcome in the critically ill patient.**

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Short title

The impact of the pH on cardiac output in the critically ill patient

Full title of trial

The impact of systemic pH on cardiac function and clinical outcome in the critically ill patient

Sponsor:	King's College Hospital NHS Foundation Trust (KCH)
Funder (s):	There are not funders
IRAS Reference	IRAS Project ID: **227870**
ISRCTN / Clinicaltrials.gov no:	It is not a trial but I am in the process of registration

Protocol Version: 3rd and Date: 26/03/2018

Full title of the research: **The impact of systemic pH on cardiac function and clinical outcome in the critically ill patient.**

IRAS Project ID: **227870**

KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work. If further arrangements have been agreed with the funder, please refer to the funding agreement and insert

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the R&I Office of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPAL INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

OTHER: add other key personal/entity responsibilities where relevant to the study

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information Governance policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

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I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of this research without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature:..... Date 06/ 03/2018

Print Name (in full): SANCHO RODRIGUEZ-VILLAR

Position: Intensive Care Medical Consultant. King´s College NHS Foundation Trust. London, UK.

CONTENTS

Full title of the research: **The impact of systemic pH on cardiac function and clinical outcome in the critically ill patient.**

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KEY WORDS

pH, cardiac contractility, acidosis, cardiac output

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CAG	Confidential Advisory Group
CI	Chief Investigator

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CRF	Case Report Form
DMC	Data Monitoring Committee
GAfREC	Governance Arrangement for NHS Research Ethics
HRA	Health Research Authority
HTA	Human Tissue Authority
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Studies Number
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File

Trial personnel

Chief Investigator

Sancho Rodriguez-Villar
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Sponsor

Liba Stones
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And

Keith Brennan
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London SE1 8WA

Statistician (if applicable)

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tel: 0034 625 981 199

Head of Department: **Dr Georg Auzinger** (Critical Care Department at King´s College)

The team of researches (all of them volunteers, including myself) who will be extracting data from medical notes, ICU charts and ICCA will be:

1. Dr Sancho Rodriguez-Villar (Consultant ICU at KINGs)
2. Dr Ashraf Molokhia (Consultant ICU at Lewisham and Greenwich NHS Trust)
3. Dr Ahmed Zaki (Consultant ICU at Lewisham and Greenwich NHS Trust)
4. Dr Paola Eiben (Clinical ICU Fellow)
5. Dr Charlotte Brathwaite Shirley (Medical ACCS)
6. Dr Priyakam Chowdhury (ST7 Anaesthesia)
7. Dr Ana Spataru (ICU Senior Clinical Fellow)
8. Dr Varsha Ramakrishnan (ICU Clinical Fellow)
9. Dr Vasile Recea (ICU Clinical Fellow)
10. Dr Pervez Khan (ICU Senior Clinical Fellow)

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11.Dr Bryony Davy (SpR Anaesthesia)

12.Dr Szilvia Szoke (ICU Clinical Fellow)

STUDY SUMMARY

STUDY OVERVIEW	
Full title	**The impact of systemic pH on cardiac function and clinical outcome in the critically ill patient**
Objectives	**Hypothesis** Titration studies in animals with normal cardiac function show that a reduction in blood pH (and presumably that of the intracellular and interstitial compartments) from the normal level of 7.40 to 7.20 is associated with a rise in cardiac output. However, when blood pH is less than 7.20, cardiac output is reduced. Similar studies in humans with or without normal cardiac function have not been done, and yet blood pH at which aggressive treatment is recommended has been set at 7.20 based solely on animal experiments. We hypothesize that a change in blood pH in humans will also affect cardiac function, but the level of blood pH at which this is observed might be similar or different in humans. In addition, the presence or absence of

	underlying cardiac disease and the type of acid-base abnormality present might modify the response of the heart to changes in blood pH. **Goals** *Primary* 1. Assess whether there are significant changes in cardiac function associated with changes in blood pH. 2. Relate the changes in cardiac function to presence or absence of underlying cardiac disease. *Secondary* 3. To establish which factors affected by blood pH have an impact on cardiac function. 4. Study the mortality of patients admitted to the Intensive Care Unit (ICU) who had continuous cardiac monitoring at any time during their admission and relate it to changes in blood pH.
Type of trial	It is not a trial
Trial design and methods	It is not a trial
Health condition(s) or problem(s) studied	It is not a trial
Target sample size	Taking into account that the primary objective of the study is to

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	analyze the relationship between the quantitative variables: change in pH and change in Cardiac Contractility, assuming an alpha risk of 5% (95% confidence level), a 20% beta risk (power of 80%) and a minimum ratio that has an estimated clinical significance with a correlation coefficient of 1.5, a bilateral estimate of sample size of 346 subjects is obtained. Assuming a 5% loss (17 individuals) during the study a total of 363 cases would be necessary.
Trial design and methods	It is not a trial
Trial duration per participant:	It is not a trial
Main inclusion/exclusion criteria:	**EXCLUSION CRITERIA** • **Atrial or ventricular arrhythmia:** you need a stable pulse to measure the contour. • **Aortic, mitral or tricuspid valve insufficiency.** In the case of valve insufficiency the valve does not close correctly. Therefore, the thermodilution curve is affected by indicator regurgitation, resulting in a prolonged indicator decay time. • **Intra-Aortic Balloon pump:** once again, the pulse contour is all wrong; but you can still get thermodilution cardiac output measurements. • **Aortic aneurysm:** the contour will be bizarre because the arterial compliance is going to be weird, with the aortic aneurysm acting as a damping system by absorbing all the pressure wave. • **Extracorporeal circuit:** when you are on bypass, there is no real arterial waveform • **Pneumonectomy:** PiCCO relies on there being a relatively normal pulmonary vasculature**.** • **Massive pulmonary embolism:** as above; it is essentially a pneumonectomy by embolism. • **Intracardiac shunt:** the PA catheter will also give an inaccurate thermodilution reading. • **Less than a minimal tidal volume 6-**

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	8mL/kg • **NON-positive pressure ventilated patients:** ➢ **Why does Stroke Volume Variation only apply to positive pressure ventilated patients?** It still applies in spontaneously breathing patients; however it is a poorer predictor of fluid responsiveness. ➢ Why? **The sensitivity is decreased: its only 63%.** The spontaneous breathing efforts draw a smaller tidal volume, and from such minor changes in thoracic pressure there would insufficient change in ventricle loading; so there may still be changes to stroke volume, but they would be tiny and difficult to measure. ➢ **- If there is profound hypovolemia, the IVC can collapse on inspiration.** Obviously this decreases preload, and confuses your SVV. You cannot predict fluid responsiveness this way, because you never get an accurate impression of preload. ➢ **- In spontaneous respiration, inspiraton increases the right venticular preload,** which means the right ventricular filling is likely still appear adequate even if there is some hypovolemia. In spite of low overall volume, the right ventricular preload remains adequate, and thus at least one of the ventricles is likely to be operating in the

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	preload-independent straight part of the Frank-Starling curve • **Severe obesity:** In obese patients, Extravascular Lung Water Index (EVLWI) is underestimated because it is related to the body weight.
Statistical methodology and analysis:	**Statistical methods** The description of quantitative variables is carried out with central tendency and dispersion indices, whether based on values (mean and standard deviation) or on ordinations (median and interquartile range) according to whether they meet normality or not, respectively. Its graphic representation is done with Histograms and Cash Diagrams. The description of categorical variables is performed with absolute and relative frequencies in percentages. Its graphic representation is done with bar charts. The relationship between categorical variables is analyzed by comparing proportions with the Pearson Chi-square test, provided that there are less than 20% of squares in the contingency table with expected frequencies less than 5. In the case that there is more 20% of squares with expected frequencies less than 5, the Fisher's exact test is used bilaterally.

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	The magnitude of the effect of the relationship between two binary variables has been analyzed with the Ratios of proportions or Relative Risk and with the Odds Ratio. The relationship between a binary exposure variable and a quantitative response is analyzed with the Student-Fisher t test for independent samples if the normality condition is met. According to whether or not the equality of variances are met, the Student-Fisher t test is used for independent groups for homogeneous variances or for non-homogeneous variances, respectively. In case of not fulfilling the condition of normality, the comparison of two means is made with the non-parametric Mann-Whitney U test. The comparison between a polytomic predictor and a quantitative response is made through the analysis of variance (ANOVA) in the case of meeting the conditions of normality and homogeneity of variances. If any of these conditions is not met, it is done with the non-parametric H test of Kruskal-Wallis. If the polytomic predictor is ordinal, the ANOVA trend test or the non-parametric Jonckheere-Terpstra trend test is also used, depending on whether normality is met or not, respectively.

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	The relationship between two independent quantitative variables is evaluated with the correlation coefficient r of Pearson if normality is met, or with the nonparametric correlation coefficient rho of Spearman if normality is not met. Its graphic representation is made with the scatter diagrams or points. Normality is assessed with the Kolmogorov-Smirnov test with the Lilliefors significance correction for large samples, or with the Shapiro-Wilks test for small samples. The equality of variances is analyzed with the Levene variance homogeneity test. The relationship between two related quantitative variables is performed using the Student-Fisher t-test for related samples in case the normality condition is met. Otherwise, the non-parametric Wilcoxon T test is used. The relationship between two paired categorical variables is performed by the McNemar symmetry test. The relationship between a continuous quantitative response and one or several predictors, whether binary, polytomic or quantitative, is done with Simple or Multiple Linear Regression

	respectively. The polytomous predictors variables are introduced in the Linear Regression models broken down into binary indicator variables coded with respect to the first reference category. An estimative multivariate linear regression model of the effect of the predictor Change of pH (between the lowest and highest pH) on the response Change in cardiac output (corresponding to the moments between the lowest and the highest pH) has been performed. The possible role as confounding factors of several variables on this relationship has been evaluated. A predictive multivariate model of linear regression has been performed to evaluate the factors that intervene in the Cardiac Contractility. Both the predictive and the estimative models have been carried out with the manual backward step procedure using the criterion of decreasing statistical significance to establish the order to evaluate the withdrawal or permanence of each predictor. In the multivariate predictive linear regression model, the criterion of statistical significance was used to decide the maintenance or withdrawal of the predictors in each step. They

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	remain in the model if they are significant and are removed from the model if they are not significant. In the multivariate models of linear regression, the criterion of clinical significance has been used to decide on the maintenance or withdrawal of the predictors in each step. They remain in the model if they produce a change greater than 10% in the coefficient of the predictor of interest (presence of confounding bias) and withdraw if the change is less than 10% (absence of confounding bias). The conditions of application of the simple or multiple linear regression (linearity, independence, normality and equality of variances) are evaluated by analysing the residuals. Values of P <0.05 are considered significant. The statistical treatment has been performed the statistical package SPSS, version 18 (SPSS Inc, Chicago, IL, USA).
STUDY TIMELINES	
Study Duration/length	Approximately 6 months
Expected Start Date	April 2018
End of Study definition and	Expected on November 2018

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anticipated date	
Key Study milestones	March study submission April 2018 start of data collection October –November data analysis
STORAGE of SAMPLES (if applicable)	No applicable
Human tissue samples	No applicable
Data collected / Storage	Observational data will be **completely anonymous** before digital storage and sending for analysis. Previous to that, it will be collected on paper form which will be encrypted coded.

1 INTRODUCTION

Why?

We would like to perform an analysis of the relationship between systemic pH and cardiac function and clinical outcome in critically ill patients in patients hospitalized the Intensive Care Unit.

How is it of relevance and importance to patients and public?

Studying this subject we could provide important information about the impact of systemic pH on cardiac function and clinical outcome in seriously ill patients and enable the clinician to

understand the best treatment of these patients. Patients will be studied who had cardiac monitoring during their ICU admission and an acid-base metabolic disorder. We exclude those patients with cardiac history or who presented an acute coronary syndrome during ICU admission.

IT IS NOT A THERAPEUTIC STUDY. ONLY OBSERVATIONAL. NO INTERVENTIONS.

Where?

In seven different ICU´s between King´s College NHS Foundation Hospital and Lewisham and Greenwich NHS Trust

How?

The study will take approximately six month to collect prospectively data from each unit. The data will be extracted from the medical notes and ICU charts. No active involvement with participants.

2 BACKGROUND AND RATIONALE

3 OBJECTIVES

Goals

Primary

1. Assess whether there are significant changes in cardiac function associated with changes in blood pH.
2. Relate the changes in cardiac function to presence or absence of underlying cardiac disease.

Secondary

3. To establish which factors affected by blood pH have an impact on cardiac function.

4. Study the mortality of patients admitted to the Intensive Care Unit (ICU) who had continuous cardiac monitoring at any time during their admission and relate it to changes in blood pH.

4 STUDY DESIGN

- Study population and groups: those patients on haemodynamic monitoring in ICU (PiCCO monitoring)

- **Calculation of the sample size:**

Taking into account that the primary objective of the study is to analyze the relationship between the quantitative variables: change in pH and change in Cardiac Contractility, assuming an alpha risk of 5% (95% confidence level), a 20% beta risk (power of 80%) and a minimum ratio that has an estimated clinical significance with a correlation coefficient of 1.5, a bilateral estimate of sample size of 346 subjects is obtained. Assuming a 5% loss (17 individuals) during the study a total of 363 cases would be necessary.

- **Statistical methods:**

The description of quantitative variables is carried out with central tendency and dispersion indices, whether based on values (mean and standard deviation) or on ordinations (median and interquartile range) according to whether they meet normality or not, respectively. Its graphic representation is done with Histograms and Cash Diagrams. The description of categorical variables is performed with absolute and relative frequencies in percentages. Its graphic representation is done with bar charts.

The relationship between categorical variables is analyzed by comparing proportions with the Pearson Chi-square test, provided that there are less than 20% of squares in the contingency table with expected frequencies less than 5. In the case that there is more 20% of squares with expected frequencies less than 5, the Fisher's exact test is used bilaterally.

The magnitude of the effect of the relationship between two binary variables has been analyzed with the Ratios of proportions or Relative Risk and with the Odds Ratio.

The relationship between a binary exposure variable and a quantitative response is analyzed with the Student-Fisher t test for independent samples if the normality condition is met. According to whether or not the equality of variances are met, the Student-Fisher t test is used for independent groups for homogeneous variances or for non-homogeneous variances, respectively. In case of not fulfilling the condition of normality, the comparison of two means is made with the non-parametric Mann-Whitney U test.

The comparison between a polytomic predictor and a quantitative response is made through the analysis of variance (ANOVA) in the case of meeting the conditions of normality and homogeneity of variances. If any of these conditions is not met, it is done with the non-parametric H test of Kruskal-Wallis. If the polytomic predictor is ordinal, the ANOVA trend test or the non-parametric Jonckheere-Terpstra trend test is also used, depending on whether normality is met or not, respectively.

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Normality is assessed with the Kolmogorov-Smirnov test with the Lilliefors significance correction for large samples, or with the Shapiro-Wilks test for small samples. The equality of variances is analyzed with the Levene variance homogeneity test.

The relationship between two related quantitative variables is performed using the Student-Fisher t-test for related samples in case the normality condition is met. Otherwise, the non-parametric Wilcoxon T test is used. The relationship between two paired categorical variables is performed by the McNemar symmetry test.

The relationship between a continuous quantitative response and one or several predictors, whether binary, polytomic or quantitative, is done with Simple or Multiple Linear Regression respectively.

The polytomous predictors variables are introduced in the Linear Regression models broken down into binary indicator variables coded with respect to the first reference category.

An estimative multivariate linear regression model of the effect of the predictor Change of pH (between the lowest and highest pH) on the response Change in cardiac output

(corresponding to the moments between the lowest and the highest pH) has been performed. The possible role as confounding factors of several variables on this relationship has been evaluated. A predictive multivariate model of linear regression has been performed to evaluate the factors that intervene in the Cardiac Contractility.

Both the predictive and the estimative models have been carried out with the manual backward step procedure using the criterion of decreasing statistical significance to establish the order to evaluate the withdrawal or permanence of each predictor.

In the multivariate predictive linear regression model, the criterion of statistical significance was used to decide the maintenance or withdrawal of the predictors in each step. They remain in the model if they are significant and are removed from the model if they are not significant.

In the multivariate models of linear regression, the criterion of clinical significance has been used to decide on the maintenance or withdrawal of the predictors in each step. They remain in the model if they produce a change greater than 10% in the coefficient of the predictor of interest (presence of confounding bias) and withdraw if the change is less than 10% (absence of confounding bias).

The conditions of application of the simple or multiple linear regression (linearity, independence, normality and equality of variances) are evaluated by analysing the residuals.

Values of P <0.05 are considered significant. The statistical treatment has been performed the statistical package SPSS, version 18 (SPSS Inc, Chicago, IL, USA).

5 STUDY SCHEDULE

Approximately:

- April 2018: Start collecting data from patient already in the ICU with the inclusion criteria.
- April 2018- September 18 approximately until reach the minimum number of 360 patients
- October-November 18 data analysis

6 CONSENT

We believe need for individual patient or personal/legal rep consent should be waived. The following aspects, needed for seeking informed consent to access patients' records, are considered disproportionate to this observational study: the difficulty, or even impossibility, of locating and contacting all patients; the high costs and effort needed; the risk of bias (Al-Shahi et al., 2005; McKinney et al., 2005; Jousilahti et al., 2005); and the very low risk of breaching individuals' privacy. In addition, strict and thorough strategies will be put in place data protection and confidentiality. Moreover, the British public has been found to be highly supportive of the use of personal medical data in non-commercial medical research which "has no effect on the individuals being studied and has been approved by an accredited research ethics committee" (Peto et al., 2004, p. 1030). Therefore, consent will not sought.

ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

- Over 16 years old- 65 years old
- On cardiac monitoring (PiCCO device)

7.2 Exclusion Criteria

EXCLUSION CRITERIA

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- **Atrial or ventricular arrhythmia:** you need a stable pulse to measure the contour.
- **Aortic, mitral or tricuspid valve insufficiency.** In the case of valve insufficiency the valve does not close correctly. Therefore, the thermodilution curve is affected by indicator regurgitation, resulting in a prolonged indicator decay time.
- **Intra-Aortic Balloon pump:** once again, the pulse contour is all wrong; but you can still get thermodilution cardiac output measurements.
- **Aortic aneurysm:** the contour will be bizarre because the arterial compliance is going to be weird, with the aortic aneurysm acting as a damping system by absorbing all the pressure wave.
- **Extracorporeal circuit:** when you are on bypass, there is no real arterial waveform
- **Pneumonectomy:** PiCCO relies on there being a relatively normal pulmonary vasculature**.**
- **Massive pulmonary embolism:** as above; it is essentially a pneumonectomy by embolism.
- **Intracardiac shunt:** the PA catheter will also give an inaccurate thermodilution reading.
- **Less than a minimal tidal volume 6-8mL/kg**
- **NON-positive pressure ventilated patients:**
  - **Why does Stroke Volume Variation only apply to positive pressure ventilated patients?** It still applies in spontaneously breathing patients; however it is a poorer predictor of fluid responsiveness.
  - Why? **The sensitivity is decreased: its only 63%.** The spontaneous breathing efforts draw a smaller tidal volume, and from such minor changes in thoracic pressure there would insufficient change in ventricle loading; so there may still be changes to stroke volume, but they would be tiny and difficult to measure.
  - **- If there is profound hypovolemia, the IVC can collapse on inspiration.** Obviously this decreases preload, and confuses your SVV. You cannot predict fluid responsiveness this way, because you never get an accurate impression of preload.
  - **- In spontaneous respiration, inspiraton increases the right venticular preload,** which means the right ventricular filling is likely still appear adequate even if there is some hypovolemia. In spite of low overall volume, the right ventricular preload remains adequate, and thus at least one of the ventricles is likely to be

operating in the preload-independent straight part of the Frank-Starling curve

- **Severe obesity:** In obese patients, Extravascular Lung Water Index (EVLWI) is underestimated because it is related to the body weight.

7 RECRUITMENT

The recruitment section may include:

- Method for identifying and recruiting participants for the study: mechanical screening. It will be done daily by researcher in each ICU. Those patient on cardiac monitoring (PiCCO device).
- Who will identify and approach participants for consent: Not needed

8 STATISTICAL METHODS

The description of quantitative variables is carried out with central tendency and dispersion indices, whether based on values (mean and standard deviation) or on ordinations (median and interquartile range) according to whether they meet normality or not, respectively. Its graphic representation is done with Histograms and Cash Diagrams. The description of categorical variables is performed with absolute and relative frequencies in percentages. Its graphic representation is done with bar charts.

The relationship between categorical variables is analyzed by comparing proportions with the Pearson Chi-square test, provided that there are less than 20% of squares in the contingency table with expected frequencies less than 5. In the case that there is more 20% of squares with expected frequencies less than 5, the Fisher's exact test is used bilaterally.

The magnitude of the effect of the relationship between two binary variables has been analyzed with the Ratios of proportions or Relative Risk and with the Odds Ratio.

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Both the predictive and the estimative models have been carried out with the manual backward step procedure using the criterion of decreasing statistical significance to establish the order to evaluate the withdrawal or permanence of each predictor.

In the multivariate predictive linear regression model, the criterion of statistical significance was used to decide the maintenance or withdrawal of the predictors in each step. They remain in the model if they are significant and are removed from the model if they are not significant.

In the multivariate models of linear regression, the criterion of clinical significance has been used to decide on the maintenance or withdrawal of the predictors in each step. They remain in the model if they produce a change greater than 10% in the coefficient of the predictor of interest (presence of confounding bias) and withdraw if the change is less than 10% (absence of confounding bias).

The conditions of application of the simple or multiple linear regression (linearity, independence, normality and equality of variances) are evaluated by analysing the residuals.

Values of $P < 0.05$ are considered significant. The statistical treatment has been performed the statistical package SPSS, version 18 (SPSS Inc, Chicago, IL, USA).

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9 PATIENT AND PUBLIC INVOLVEMENT (PPI)

The impact of changes in acidity on clinical outcome and cardiac function has been examined in small numbers of patients in the past. However, its relevance to the monitoring and treatment of larger number of patients is unclear. This study should provide important information using a large cohort of patients.

10 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the KCH R&I Office, and deemed sufficient to cover the requirements of the study.

THIS STUDY IS NOT FUNDED

11 DATA HANDLING AND MANAGEMENT

Where data will be recorded: initially on paper with a reference code for each patient. On enrolment the patient is given a unique study ID. This usually has a numeric code for the site as well as a sequential number for patients e.g 23-001, 23-002 etc. the case report forms (data collection forms) only have study ID on. There is no patient ID at all on the CRF, but we have an enrolment log- just a list of name, hospital number and study ID.

12 MATERIAL/SAMPLE STORAGE

There is usually a copy of this in the site file and on our network drive. This is only accessible by appropriate hospital staff and outside researchers only if patient consents. Therefore research team knows who the number relates to and could trace back if necessary but no-one else. This is why we refer to an enrolment log in the IRAS form because we need some way of linking patients to data.

- If samples will be stored for future use (and the details): data will be store for about six months. There is usually a copy of this in the site file and on our network drive.
- Measures for the processing, control and safe storage of samples: no tissue samples.
- Details of data controller/custodian. It will be Chief investigator , myself (Sancho Rodriguez-Villar)

NOT APPLICABLE :In the study, will be collected from patients in accordance with the patient consent form and patient information sheet and shall include all tissue samples or other biological materials and any derivatives, portions, progeny or improvements as well as all patient information and documentation supplied in relation to them. Samples will be processed, stored and disposed in

accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter.

13 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by KCH R&I.

Choose either (having discussed with the KCH R&I Office):

- This study has been peer reviewed within KCH/KCL, by an independent and relevant peer reviewer/committee (amend as required) on (insert date). The Sponsor has accepted these reviews as adequate evidence of peer review.

14 ASSESMENT AND MANAGEMENT OF RISK

No applicable

15 RECORDING AND REPORTING OF EVENTS AND INCIDENTS

16.1 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

15.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

Full title of the research: **The impact of systemic pH on cardiac function and clinical outcome in the critically ill patient.**

IRAS Project ID: **227870**

16.2.1 Severity: NOT APPLICABLE

The generic categories below are given for use as a guide. You may have a more specific scale that you want to use related to the disease (e.g. CTCAE criteria).

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

16.2.2 Causality: N/A. NOT APPLICABLE

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

If a differentiated causality assessment which includes other factors in the study is deemed appropriate, please add/amend the following wording to specify:

It is of particular importance in this study to capture events related to the product application procedure (specify e.g. surgery) / product failure / mandatory concomitant medications (specify e.g. conditioning chemotherapy). The assessment of relationship of an adverse event to this/these additional safety issue(s) will also be carried out as part of the study.

The differentiated causality assessments will be captured in the study specific CRF/AE Log and/or SAE form (amend as required).

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely

Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

16.2.3 Expectedness: N/A. NOT APPLICABLE from the observational study

Category	Definition
Unexpected	An adverse event which is not consistent with the information about the procedure listed in the manual of operation or clearly defined in this protocol.

* this includes listed events that are more frequently reported or more severe than previously reported

15.3 Recording adverse events: N/A

NOT APPLICABLE. COLLECTION OF DATA ONLY

15.4 Procedures for recording and reporting Serious Adverse Events: N/A. NOT APPLICABLE

All serious adverse events will be recorded in the medical records and the CRF, and the sponsor's AE log. All SAEs (except those specified in section 16.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete an SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Where the event is unexpected and thought to be related to the procedure this must be reported by the Investigator to the Health Research Authority within 15 days.

Full title of the research: **The impact of systemic pH on cardiac function and clinical outcome in the critically ill patient.**

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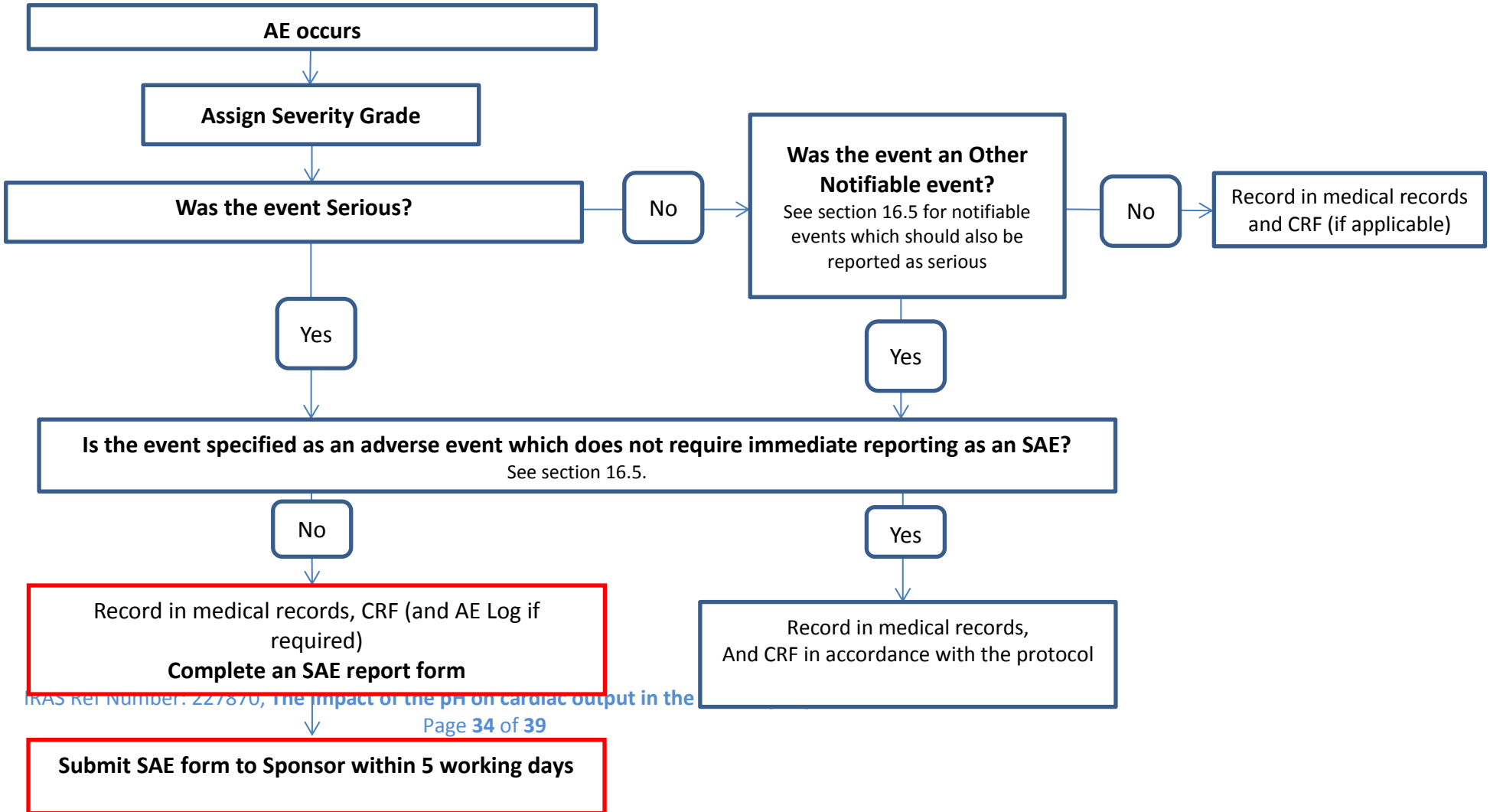
Flow Chart for SAE reporting



16.5 Serious Adverse Events that do not require reporting

It is an observational study. We do not expect any incident. There are not interventions at all. If a SAE occurs (from PiCCO monitoring use) will report to the Clinician Consultant in charge who is at the end the final responsible of the patient and the responsible of putting the PiCCO monitoring on the patient.

15.6 Reporting Urgent Safety Measures

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

15.7 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

The CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

16.8 Reporting incidents involving a medical device

Any adverse incident involving a medical device should be reported to the manufacturer of the device.

This is especially important where the incident has led to or, was it to occur again could lead to an event classified as serious (see section 9.1 for definition of SAE). Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.

All adverse incidents must be reported by the Clinician Consultant responsible of the patient. The study is only observational and there are not interventions or decisions involving the use of the PiCCO device. That decision will be made by the Clinical Consultant in charge in the ICU therefore incidents should be reported as soon as possible (usually within 24 hours) as per protocol in the Trust.

Adverse incidents related to a medical device can be reported directly to the MHRA via the online system (www.mhra.gov.uk). Alternative contact details: Medicines & Healthcare products Regulatory Agency Adverse Incident Centre (Tel: 020 7084 3080; Fax 020 7084 3109).

Local trust reporting procedures may also need to be followed. It is the responsibility of the PI and study site team to ensure they are aware of any specific local requirements for reporting device incidents.

15.9 Trust incidents and near misses. NOT APPLICABLE from the observational study

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.
A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

16 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

17 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

The training section may also include:

- Specific training requirements for staff working on the project: NOT APPLICABLE
- Specific qualifications and experience required of staff on the project: SENIOR ICU STAFF
- Identifying if training may require a renewal at any point throughout the study: NOT APPLICABLE

18 INTELLECTUAL PROPERTY: N/A. NOT APPLICABLE

19 INDEMNITY ARRANGEMENTS

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the Joint Research Office.

20 ARCHIVING

Date of birth	
Sex (M/F)	
Hospital ADMISSION date	
ICU ADMISSION date • Unplanned/emergency admission. • Planned /elective admission.	
ICU DISCHARGE date	
Discharged alive from ICU? • From ICU to home directly. • From ICU to hospital ward. • From ICU to another ICU (other hospital)	**(Y / N)**
Discharged alive from HOSPITAL? • Home • Nursing home or equivalent	**(Y / N)**
28-day mortality. Death occurring within 28 days of hospital discharge?	**(Y / N)**

Admitting diagnosis group:
• Cardiac arrest/ other causes of cardiogenic shock
• Cardiothoracic surgery
• Septic shock
  ➢ Medical
  ➢ Neutropenic sepsis/ other haematology & oncology sepsis
  ➢ Surgical
• Post-operative management: any other speciality	

• Haemorrhagic shock
  ➢ Major trauma
  ➢ Gastrointestinal/other medical
  ➢ Post-surgical
• Acute respiratory failure
  ➢ COPD /asthma exacerbation
  ➢ Pneumonia
  ➢ Other causes
• Acute renal failure requiring hemofiltration
• Trauma/neuro-surgical
• Decompensated liver disease/ acute liver failure
• Diabetic ketoacidosis/hyperosmotic syndrome
• Others	

PATIENT RESEARCH ENCRYPTED CODE:	

Chronic diseases
• Ischaemic heart disease.
• Congestive heart failure
• Atrial fibrillation/Atrial flutter
• Devices
  ➢ Pacemaker (PM) +/- Implantable cardioverter-defibrillator (ICD)
  ➢ Cardiac resynchronization therapy (CRT) +/- (ICD)
• Arterial hypertension
• Pulmonary hypertension
• Pulmonary embolus/deep vein thrombosis
• COPD/Asthma
• Fibrosis
• Diabetes mellitus
• End stage kidney disease (on regular dialysis)
• Chronic kidney disease or pre-dialysis (NOT on dialysis)
• Liver disease
• Morbid obesity.
• Recent quimiotherapy / radiotherapy (last 30 days)
• Haematology malignancies
  ➢ Acute myeloid leukaemia (AML)
  ➢ Chronic lymphocytic leukaemia (CLL)
  ➢ Myeloma
  ➢ Lymphoma
• Other hemato-onco malignancies	

Severity scores • APACHE II	

21 PUBLICATION AND DISSEMINATION POLICY

PUBLICATION IN PEER REVIEW JOURNALS

22 REFERENCES

- Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. First of two parts. N Eng J Med 1998; 338:26-34.
- Cingolani HE, Faulkner SL, Mattiazzi AR et al. Depression of human myocardial contractility with "respiratory" and "metabolic" acidosis. Surgery 1975; 77:427-432.
- Shapiro JL. Pathogenesis of cardiac dysfunction during metabolic acidosis: therapeutic implications. Kidney Int 1997; Supl 61:S47-S51.

23 APPENDICES

No appendices

Appendix 1: PROTOCOL VERSIONS

Version Stage	Versions No 3rd	Version Date 26/03/18	Appendix No detail the reason(s) for the protocol update