Measurement of Heart Rate Variability in critically ill patients: Refinement of data acquisition and analysis

IRAS ID 254530

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Study Synopsis and Summary

Title	**Measurement of Heart Rate Variability in critically ill patients: Refinement of data acquisition and analysis**
Protocol short title / Acronym	
Protocol Version number and Date	Version 1.9 (2nd February 2019)
IRAS	254530
Study Phase if not mentioned in title	Prospective observational feasibility study
Is the study a Pilot?	Yes – this is Pilot feasibility study
Study Duration	12 months
Methodology	Prospective observational feasibility study
Sponsor	University of Liverpool
UK legal representative	University of Liverpool
Chief Investigator	Prof. Dr. med. Ingeborg Welters
REC number	
Medical condition under investigation	Critical illness
Purpose of clinical trial	To investigate if two devices to monitor and capture Heart Rate Varibility (HRV) and ECG data in Critically ill patients produce comparable results.
Primary objective	To describe the robustness of data on HRV obtained by two different monitoring systems during daily care of critically ill patients.
Secondary objective	1. To identify the most suitable and cost-efficient device for HRV monitoring in critically ill patients. 2. To define amendments in data capture and analysis required to proceed to a larger clinical trial
Number of Subjects	30 patients

Trial Design	Prospective observational feasibility study
Endpoints	**Primary outcome:** • Number of interpretable HRV epoch episodes for each device and comparison between Isansys device and gold-standard holter monitoring (Isansys and Holter Monitor) **Secondary outcomes:** • Correlation of HRV time domain, frequency domain and non-linear HRV measures analysis between Isansys wireless monitoring patch and Holter monitoring • Correlation between HRV and onset of arrhythmias • Correlation between HRV and cardiorespiratory events (desaturation, drop in blood pressure >20%, change in ventilator settings) • Nurses' and medical staff's perception of the usability of both monitoring systems in daily routine practice
Main inclusion and Exclusion Criteria	**Inclusion criteria:** • Adult patients ≥18 years • Expected stay in the ICU >48 hours • Sinus rhythm on ITU admission • Mechanically ventilated patients **Exclusion criteria:** • Non-ICU patient • History of Atrial Fibrillation • Inability to obtain consent
Randomization	Not applicable
Study procedure	If all inclusion criteria are met and no exclusion criteria are present, patients will be eligible, invited to participate and informed consent will be sought. Continuous ECG data will be recorded using two different devices. ECG data will then be processed to derive HRV using the methodology

	described by the European Society of Cardiology Taskforce guidelines.[2] Continuous 24 hour ECG recording with be divided into 5 minute epochs and short term HRV measures will be calculated, in the time domain, frequency domain and non-linear domains. Entire 24 hour ECG recordings will also be used to calculate long term HRV measures in the time domain, frequency domain and non-linear domains as described elsewhere.[2] HRV data will be analysed as decribed in the statistical methodology and analysis section. HRV data will be analysed by the Medical Engineering and Clinical Physics Department of the Royal Liverpool and Broadgreen University Hospital. In addition, routinely available clinical and laboratory parameters will be collected from enrollment until day 14, day of discharge from ICU or day of death (whatever occurs first). There will be no change in clinical practice and no additional procedures undertaken or medications administered. After the patient has left the ICU, medical and nursing staff involved in the care of the patient will be asked to fill in a questionnaire on their experience with both monitoring systems.
Statistical Methodology and Analysis	RR interval data from the Isansys patch will be downloaded onto an Excel spreadsheet. The RR interval will be uploaded to Mathlab. The Medical Engineering and Clinical Physics department have developed a program in the Mathlab environment for analysis and output of HRV data. ECG data will undergo preprocessing to remove artefacts and ectopic beats and be analysd using the Ornstein-Uhlenbeck third-order Gaussian process applied to the heart rate/RR interval.[11] This technique has been developed by the Medical Engineering and Clinical Physics department. Once the ECG has been preprocessed HRV will be derived according to the European Society of Cardiology

	guidelines.[2] We will use time domain measures, frequency domain measures and Non-linear measures such as the Poincare plot. HRV data will be analysed statistically as described below. Comparision between devices will be assessed by Bland-altmann methodology. If the difference between the Isansys monitor and the holter monitor is sufficiently small not to cause problems in the clinical interpretation (within 95% limits of agreement), then the Isansys wireless device can be considered to be interchangeable with the gold-standard holter monitoring device. Descriptive statistics showing means ± standard deviation (SD) for continuously distributed variables, and number and proportions for categorical variables will be used for all comparisons. Chi-square tests will be used for categorical outcomes unless assumptions of the test are found to have been violated, in which case Fisher's exact test will be used. Parametric and nonparametric methods, as determined by the distribution of each variable, will be used to test statistical significance of continuous variables. Logistic regression will be utilized to assess the predictive value of HRV different outcomes (onset of arrhythmias, change in ventilatory setting, drop in blood pressure, desaturation) adjusting for covariates. Bland-altmann methodology will be used to assess the comparability of results between each HRV monitoring device (Isansys and Holter monitor).

Abbreviations used in study protocol

AF	Atrial Fibrillation
CRF	case report form
CRP	C-reactive protein
ECMO	extracorporeal membrane oxygenation
GCP	Good Clinical Practice
GP	General Practioner
HRV	Heart Rate Variability
HF	High Frequency Domain
IQR	Interquartile Range
ICU	intensive care unit
LOS	Length of stay
LV	Left ventricle
LA	Left atrium
LF	Low frequency domain
LF/HR	Low frequency/High Frequency ratio
NN	Normal-Normal Interval
pNN50	Percentage of RR intervals that differ by greater than 50ms
RCT	randomized controlled trial
REC	Research Ethics Committee
RR	R-R Interval
RMSSD	Root mean square of successive RR intervals
SAPS	Simplified Acute Physiology Score
S	Area of elipse of Poincre plot which represents total HRV
SD	standard deviation
SD1	Poincre plot standard deviation perpendicular to the line of identity
SD2	Poincre plot standard deviation along the line of identity
SD1/SD2	Ratio of SD1 to SD2
SDNN	Standard Deviation of NN interval
SDANN	Standard deviation of the average NN interval
VLF	Very low frequency domain
ULF	Ultra low frequency domain

Glossary of Research Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
ICF	Informed Consent Form
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
TSC	Trial Steering Committee

1. Introduction

The healthy cardiovascular system is in a state of dynamic stability.[1] This stability is achieved by altering heart rate, blood pressure and other factors to react to internal and external stressors.[1] Alterations in heart rate and blood pressure is under the control of the autonomic nervous system. HRV analysis is a method used to assess cardiac autonomic function.[2] Heart rate variability analysis assesses the variability between heart beats which reflect alterations in heart rate due to fluctuations in the autonomic nervous system.[3] HRV is therefore considered a measure of neurocardiac function that reflects heart-brain interactions.[4]

Autonomic dysfunction is often seen in critically ill patients' and as part of disorders requiring admission to the intensive care unit.[5] Assessment of the autonomic nervous system may provide information regarding pathophysiology, severity and prognosis associated with these disorders.[5] Depressed HRV has been associated with increased 30-day all-cause mortality in intensive care unit patients.[6] Furthermore alterations in heart rate variability have been recognised in sepsis, multiorgan dysfunction syndrome, acute ischaemic stroke, traumatic brain injury, Gullian-Barre syndrome and following myocardial infarctions and malignant arrhythmias.[5]

HRV analysis has seen a significant increase in clinical use since the 1960's. However the significance and meaning of many different HRV measures has led to the potential for incorrect conclusions and interpretations.[2] In 1996 the European Society of Cardiology and the North American Society of Pacing and Electrophysiology published guidelines for the Standard of measurement, physiological interpretation, and clinical use of heart rate variability.[2] The goal of these guidelines was to, 'standardise nomenclature and develop definitions of terms; specify standard methods of measurement; define physiological and pathophysiological correlates; describe currently appropriate clinical applications and identify areas for future research.'[2] These guidelines continue to form the basis and define the conduct of much of the research into HRV.

The European society of cardiology guidelines recognised a number of different HRV measures. Time domain measures are the simplest method of analysis of HRV. In a continuous ECG recording, the time between adjacent R wave peaks of QRS complexes is detected. This time interval is termed the N-N interval. Simple statistical tests are then applied to the N-N interval to determine the HRV, these include the standard deviation of the N-N interval (SDNN), square root of the mean squared differences of the N-N interval (RMSSD), the number of interval differences of successive N-N intervals greater than 50ms (NN50), and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50).[2] Frequency domain measures

make use of power spectral density analysis and fast fourier transform analysis to provide information on how power distributes as a function of frequency.[2] This technique splits the ECG waveform into small subunits/epochs of time depending upon whether high frequency, low frequency or very low frequency measures are required (see below). The epochs of ECG waveform recording is then transformed from a temporal signal into a spectral representation whereby ECG signal is expressed as the sum of multiple sinusoidal waves of a given amplitude and frequency. These amplitudes are then plotted to give the power spectrum by plotting power versus frequency. Spectral components include frequencies measured HF domain(0.15-0.4Hz) thought to represent the parasympathetic input, LF domain (0.04-0.15Hz) thought to represent the sympathetic nervous system and the parasympathetic nervous system, VLF domain (<0.04Hz) and the ultra-low frequency (ULF) domains (<0.003Hz).[27] Measurement of the frequencies can be made in absolute values, but are often recorded as normalised units which represents the relative value of each power component in proportion to the total power minus the VLF component.[82] Non-linear methods include measures such as the Poincare plot.[2] In the Poincare plot an individual's N-N interval is plotted against time and standard deviation used to interpret changes.[9] The Poincare plot is described by two descriptors, SD1 is the fast beat-to-beat variability in the R-R intervals whilst SD2 describes the longer variability.[9,2] SD1 reflects mainly the parasympathetic component of the autonomic nervous system, whilst SD2 reflects the parasympathetic and sympathetic components.[9]

A recent systematic review of the use of HRV evaluated the methodology and design of HRV studies in critical care.[3] Karmali et al revealed that over 230 studies have been published considering HRV in critical care.[3] These studies published in the critical care literature differed vastly in trial design, methodology, confounding and data was inconsistently reported.[3] Details on the time duration of recordings, epochs used in analysis and patient position was not reported in the majority of studies.[3] Furthermore, many of the studies did not detail methods to detect artefact or describe how artefact was managed.[3] These are significant failings, as ECG recording in the critically ill frequently suffers interference and physiological artefacts.[3] Variability analysis should be free from artefact and suffer minimal noise:signal ratio.[10] Artefact removal for HRV analysis often requires premature atrial beat or ventricular ectopic beat removal and appropriate interpolation of ECG QRS complexes. Alternatively techniques such as Poincare have been developed to allow automatic identification and removal of artefact.[10]

Each technique for the measurement of HRV represents a unique and distinct means of characterising a series of data in time.[10] However, a number of factors can affect HRV measures regardless of the technique used. Standing and head up tilt are known to increase sympathetic activity. Similarly deep breathing and sighs have been shown to alter HRV indices as have alterations in blood pressure and the baroreflex.[10] These factors should be taken into account

irrespective of what measurement technique is employed. The duration of measurement for analysis should also be taken into account. Dependent upon analysis technique the duration of measurement can range from 2 minutes to 24 hours. There remains significant debate as to the optimal duration of measurement, but in general terms this should be suitable for the technique and explained fully in studies.[10,2] Despite the number of studies using HRV in critical care there remains significant heterogeneity in methodology.[3] This uncertainty has led to the need to clarify the factors that can impact upon HRV recording and analysis in the critically ill population. Karmali et al highlight the need for consensus guidelines relevant to critical care medicine.[3] The present study hopes to address these issues and compare the robustness of HRV measures obtained from two separate devices under consideration for use in further research at the Royal Liverpool University Hospital.

The devices to be used in this study will be:

1. The Isansys Lifetouch cardiac monitor is a wireless CE marked device produced by Isansys Lifecare Limited. The Isansys lifetouch cardiac monitor continuously records filtered ECG sampled at 1000Hz. ECG data is transmitted and stored in a wireless interface called the Patient Gateway and Lifeguard Server.
2. A Holter monitoring device that is CE marked and validated for medical grade continuous ECG recording. Holter monitoring is considered the gold-standard monitoring for ECG signal analysis. The Holter device will consist of a 12 lead ECG that will record continuously for 72 hours. ECG data will be recorded to a memory card and the ECG data analysed using standard software. The signal will be sampled at 1000Hz.

Whilst both monitoring devices are capable of recording continuous ECG and HRV data, it remains unclear how robust the data are with regards to interference and artefacts. In particular, it is unclear how each monitoring device will operate whilst patients are undergoing daily care maneuvers such as physiotherapy, washing and patient repositioning. Furthermore, it has not been described yet how HRV is affected by interventions such as mechanical ventilation, administration of inotropes or vasopressors, paralysis agents, or renal replacement therapy. The current study aims to elucidate the impact of these standard interventions on HRV and the robustness of HRV measurement between the Isansys wireless monitor and the gold-standard HRV monitoring techenique. This feasibility study will aide decision making with regard to which device will be most suitable for further studies of HRV in critically unwell patients.

2. Trial Objectives, Design and Statistics

2.1 Trial objectives

The **primary objective** is*:*

- To describe the robustness of data on HRV data obtained by two different monitoring systems in daily care of critically ill patients. The Isansys wireless monitoring device will be compared to the gold-standard holter monitoring device for ECG analysis.

The **secondary objectives** are:

- To identify the most suitable and cost-efficient device for HRV monitoring in critically ill patients.
- To define amendments in data capture and analysis required to proceed to a larger clinical trial
- To generate preliminary data on the variation of HRV in a critical care patients.

Primary outcome:

- Number of interpretable monitoring epochs in each HRV monitoring system after elimination of artefacts, extra beats and interference

Secondary outcomes*:*

- Correlation and comparison of HRV time, frequency and non-linear mesures between the Isansys monitoring device and the gold-standard holter monitoring system.
- Correlation between HRV and onset of arrhythmias (ventricular or atrial)
- Correlation between HRV and cardiorespitatory events that commonly occur in critically ill patients, including, oxygen desaturation (SaO2<85%), variations in blood pressure of >20%, change in ventilatory support, muscle paralysis, position of the patient, administration of vasopressors (e.g. noradrenaline and vasopressin).
- Nurses' and medical staff's perception of the usability of both monitoring systems in daily routine

2.2 Trial Design

This is a prospective observational study with no change in clinical practice.

2.3 Trial Statistics

ECG data will be downloaded from the holter device and analysis in holter device software package which derive HRV data. RR interval data from the Isansys patch will be downloaded onto an Excel spreadsheet. The RR interval will be uploaded to Mathlab. The Medical Engineering and Clinical Physics department have developed a program in the Mathlab environment for analysis and output of HRV data. ECG data will undergo preprocessing to remove artefacts and ectopic beats and be analysd using the Ornstein-Uhlenbeck third-order Gaussian process applied to the heart rate/RR interval.[11] This technique has been developed by the Medical Engineering and Clinical Physics department. Once the ECG has been preprocessed heart rate variability will be derived according to the European Society of Cardiology guidelines.[2]

We will use time domain measures, frequency domain measures and non-linear measures such as the poincre plot, approximate and sample entropy and detrended fluctuation analysis in our analysis of HRV.

Comparision between devices will be assessed by Bland-altmann methodology. The difference between measures recorded from the Holter monitor and the Isansys wireless monitor will be plotted against the average value for each HRV measure for individual patients. Any measure of relationship between the measurement error and the estimate of the true value (average of the two measurements) can be examined. If the difference between the Isansys monitor and the holter monitor is sufficiently small not to cause problems in the clinical interpretation (within 95% limits of agreement), then the Isansys wireless device can be considered to be interchangeable with the gold-standard holter monitoring device.

Heart rate variability data will be analysed statistically as described. Descriptive statistics showing means ± standard deviation (SD) for continuously distributed variables, and number and proportions for categorical variables will be used for all comparisons. Chi-square tests will be used for categorical outcomes unless assumptions of the test are found to have been violated, in which case Fisher's exact test will be used.

Parametric and nonparametric methods, as determined by the distribution of each variable, will be used to test statistical significance of continuous variables. Logistic regression will be utilized to assess the predictive value of HRV for different outcomes (mortality, ventilator free-days, length of stay, SOFA sore) adjusting for covariates.

3. Sample Size, Selection and Withdrawal of Subjects

3.1 Sample size

In this single-centre study we wish to analyse 40 consecutive patients in whom a complete set of data can be obtained. From our previous experiences the incidence of AF in our intensive care unit is approximately 13.8%. Therefore in a sample size of 40 patients we would expect 2-3 patients to develop AF. This would allow us the opportunity to investigate any correlation between the changes in HRV preceding the onset of AF and investigate our secondary objectives to inform a larger clinical trial.

3.2 Inclusion criteria

- Adult patients ≥18 years
- Expected ICU stay >48 hours
- Sinus rhythm on admission
- Mechanically ventilated patients

3.3 Exclusion criteria

Any of the following criteria:

- Non-ICU patient
- Known Atrial Fibrillation
- Dependent upon pacemaker
- Previous cardio-thoracic surgery
- Expected ICU stay <48 hours

3.4 Criteria for Premature Withdrawal

A patient may request to be withdrawn from the study at any time, for any reason, without prejudice and without an impact on their clinical care. A patient may also be withdrawn from the study at the request of his/her legal representative or clinical team, for any reason.

4. Study Procedures

4.1 Screening Procedures

Patients will be screened against the inclusion and exclusion criteria on admission to ICU.

4.2 Consent and Enrolment Procedures

Critically ill patients often have impaired capacity as a result of their underlying illness and/or sedating medications. Therefore, there will be three routes by which a patient may be enrolled in the study.

i) Patient with capacity to consent:

- The patient will be provided with a written 'Patient Information Sheet'.
- A member of the research team with a valid GCP certificate will provide verbal information and answer any questions.
- If the patient chooses to be enrolled in the study they will be asked to sign a 'Patient Consent Form'.
- The patient may withdraw consent at any stage (as explicitly stated in the 'Patient Information Sheet').

ii) Patient without capacity where a Personal Consultee is immediately available:

- When a patient does not have capacity, the research team will attempt to identify a personal consultee (in accordance with section 32 of the mental capacity act).
- The personal consultee will be provided with a written 'Personal Consultee Information Sheet'.
- A member of the research team with a valid GCP certificate will provide verbal information and answer any questions.
- The personal consultee will be asked to use their knowledge of the patient's beliefs to advise the research team as to whether or not they feel the patient would chose to enrol in the study.
- When the personal consultee feels the patient would have chosen to participate in the study they will be asked to sign a Personal Consultee Declaration Form'.
- If the Personal Consultee is unable to come to the hospital, we plan to contact them by phone. We will provide information about the study and email or fax the "Personal Consultee Information Sheet" and answer any questions. If the personal consultee feels the patient would have chosen to participate in the study, we will email or fax a 'Personal Consultee Declaration Form' and ask them to sign and send it back to us.

- The personal consultee may withdraw the patient at any stage (as explicitly stated in the 'Personal Consultee Information Sheet').
- When the patient regains capacity, the research team will speak to the patient at the earliest opportunity and ask the patient to provide consent to continue participation; if the patient chooses to continue to participate in the study they will be asked to sign a 'Consent Form (Continuation)'; if the patient gives consent, they are free to withdraw their consent at any time; if the patient does not wish to consent, they will be withdrawn from the study.
- In the event that the patient never regains capacity or dies then he/she will remain in the study and their data will be included in the final analysis.

iii) Patient without capacity where a Personal Consultee is not immediately available:

- When a patient does not have capacity and the research team are unable to identify or contact an appropriate personal consultee we will contact a Nominated Consultee.
- The nominated consultee will be a Consultant Intensivist who understands the patient's medical problems and has been informed about the study. The nominated Consultee may be the Consultant who is caring for the patient or a Consultant who is not directly involved in the clinical care of the patient. All Consultants who agree to act as nominated consultees will be listed in the site file.
- The nominated consultee will not be a member of the study team and will have no connection to the research, to the funder or to the Research Ethics Committee.
- The nominated consultee will be provided with a 'Nominated Consultee Information Sheet' and a member of the research team with a valid GCP certificate will provide verbal information and answer any questions.
- When the nominated consultee finds no reason why the patient would not have chosen to enrol in the study they will be asked to sign a 'Nominated Consultee Declaration Form'.
- The nominated consultee may request at any stage that the patient is withdrawn (as explicitly stated in the 'Nominated Consultee Information Sheet').
- When the patient regains capacity, the research team will speak to the patient at the earliest opportunity and ask the patient to provide consent to continue participation; if the patient chooses to continue to participate in the study they will be asked to sign a 'Consent Form (Continuation)'; if the patient gives consent, they are free to withdraw their consent at any time; if the patient does not wish to consent, they will be withdrawn from the study.
- In the event that the patient never regains capacity or dies then he/she will remain in the study and their data will be included in the analysis.

We will record all ECG data from admission. If a patient or consultee declines consent, the patient will be removed form the study and all data obtained so far will be destroyed. Patients, personal consultees and nominated consultees will be given 24 hours to make a decision regarding participation in the study. If patients or their personal consultees need longer to make an informed decision, this will be respected and facilitated if possible.
In situations where the personal consultee is not able to come to the hospital, we also plan to take informed consent over the phone. In this case, a member of the research team will contact the personal consultee and inform them about the study. They will be sent an information sheet by email or fax as preferred. The personal consultee will be given adequate time and opportunities to ask questions over the phone. If they agree that they are not aware of any reasons why the patient may not have wanted to participate, they will be asked to sign the declaration form and return it to the research team by email, Royal Mail or in person. When the patient regains capacity, the research team will speak to the patient at the earliest opportunity and ask the patient to provide consent to continue participation; if the patient chooses to continue to participate in the study they will be asked to sign a 'Consent Form (Continuation)'; if the patient gives consent, they are free to withdraw their consent at any time; if the patient does not wish to consent, they will be withdrawn from the study.

4.3 Schedule of study procedure

With informed consent, the following routinely recorded clinical and laboratory data will be collected:

- Baseline demographics and comorbidities
- Administration of beta blockers or anti-arrhythmics
- Administration of sedative agents (general anaesthetics/opioids/benzodiazepines)
- Reasons for admission to ICU
- Daily biochemistry and haematology results
- Severity of illness scores, including APACHE II and daily SOFA scores
- Daily CAM ICU scores / delirium
- Daily cardiac rhythm as per nursing entry or clinical diagnosis
- Daily clinical parameters, including medications (vasopressors/ionotropes/steroids/muscle relaxants) and organ support
- Daily AKI stage, including treatment with RRT

After obtaining informed consent, continuous ECG data will be recorded using the two different devices. ECG data will then be processed to derive HRV using the methodology described by the European Soceity of Cardiology Taskforce guidelines.[2] Processing of ECG data entails checking

for and removal of extrasystole and ectopic beats with interpolation of QRS complexes as described elsewhere.[2] Continuous 24 hour ECG recording will then be divided into 5 minute epochs for which short term HRV values will be calculated. HRV will be calculated in the time domain, frequency domain and non-linear domains for each 5 minute epoch. Entire 24 hour ECG recordings will be used for long term HRV measures in the time domain, frequency domain and non-linear domains as described the Taskforce guidelines.[2] HRV data will then be analysed according to that decribed in the statistical methodology and analysis section. HRV data will be calculated by the Medical Engineering and Clinical Phyics department at the Royal Liverpool and Broadgreen University Hospital. They will be blinded to any patient identifiable or clinical information.

Daily data will be collected until day 5 in ICU, day of discharge from ICU or day of death (depending on what occurs first). In addition, we will record ICU and hospital length of stay, ICU and hospital mortality and occurence of arrhythmias during ICU stay, after 30 days, and after 90 days following enrollment. Data will be collected by accessing routinely available results in the patients' medical records, and if necessary, by contacting the patient's General Practioner (GP).

There will be no change in clinical practice. Patients will not receive any therapies or interventions that they would not have received if they had not been enrolled in the study and no tissue samples will be taken.

After a participant's discharge from the ICU, the medical and nursing staff involved in the care will be asked to fill in a questionnaire to evaluate userfriendliness, interference of HRV monitoring systems with routine medical and nursing procedures and their views on using such devices in a larger clinical trial. With informed consent from the staff member, the responses will be collected and analysed.

4.4 Follow up

All patients will be followed up until day 90 after enrolment. Data will be collected by accessing routinely available information in the patients' medical records, and if necessary, by contacting the patient's GP.

4.5 End of Study Definition

The study will end after a total of 30 evaluable patients with complete data collection have been enrolled.

5. Laboratories

Not applicable

6. Assessment of Safety

6.1 Safety outcomes

We plan to collect only routinely available data. There will be no change in clinical practice. Patients will not receive any therapies or interventions that they would not have received if they had not been enrolled in the study and no tissue samples will be taken. Therefore we do not anticipate any adverse events or safety risks for patients, their personal consultees or members of the research team from participation in this study.

6.2 Safety of Heart rate variability monitoring devices

Device 1

Isansys Lifetouch Sensor is a fully CE marked medical device. The monitoring system includes single use wearable adhesive patches which are supplied in at least three sizes, depending on the age and size of the patient. Each Lifetouch provides the following clinical data continuously for a period of up to 5 days:

Heart rate
Respiration rate
Real time heart rate variability
Visualization of the ECG
3 axes accelerometer output

The Isansys Lifetouch Sensor is fully wireless and battery operated. The battery is not accessible to the patient or staff. All Isansys Lifetouch Sensor are single patient use and will be disposed off by following local procedures Information is transmitted wirelessly to a mobile patient status engine (ipad) via wifi and Low energy Bluetooth connectivity. The patient status engine Gateway is supplied in a protective medical grade bezel frame sealed in such a way to allow it to be cleaned with standard disinfecting/sterilising liquids or wipes. The device is safe with all other intensive care monitoring.

Device 2

Ambulatory Holter ECG monitoring is a standard of care used by the cardiorespiratory department. Ambulatory holter monitoring involves attaching a 12 lead ECG to the patient in the standard ECG lead configuration using standard ECG adhesive dots. Holter monitors record continuously for 72 hours onto a memory card and are entirely battery operated with no new electrical connection to the patient. Following 72 hours the memory card is analysed using software provided by the holter monitoring company. The software is of medical standard and provides HRV data, data on the number of interpretable episodes, data on ectopic beats and arrhtyhmias. Ambulatory holter monitoring is already in routine clinical use within the Royal Liverpool and Broadgreen University Hospital. They are CE marked and validate for use on patients.

6.3 Ethics Reporting

Approval from a Research & Ethics Committee (REC) will be sought. The REC will be informed about any changes according to the official National Research Ethics System regulations.

7. Steering Committee

	Name	Institution
1		
2		
3		
4		
5		
6		

8. Data safety and monitoring board

This is an observational study with no change in clinical practice. A Data safety and monitoring board will not be established.

9. Ethics & Regulatory Approvals

The study will be submitted centrally for consideration by a NRES approved Research Ethics Committee.

10. Data Handling

10.1 Confidentiality:

- All enrolled patients will have their hospital identification number and name recorded on a master list which will be held in a locked office in the Intensive Care Department. Only members of the study team will have access to the master list.
- All enrolled patients will be allocated a unique study number which will be used for referencing all of the data recorded.
- The Chief Investigator will act as 'Custodian' for all data collected.
- No patient identifiable details will be transferred outside the EU.
- No patient identifiable details will be included in the published study reports.
- All HRV analysis will be undertaken by the Medical Engineering and Clinical Physics department at the Royal Liverpool University Hospital. All data sent for analysis will be fully anonymised ECG data that will be coded with the unique study number. The Medical Engineering and Clinical Physic department will not have any patient identifiable information or access to patients clinical notes or information.
- Clinicians caring for the patient will have no access to the HRV data and all data analysis of Heart Rate Variability will be undertaken following discharge of the patient from the ICU

Information provided to General Practitioners:

- The patient's general practitioner (GP) will only be informed about the patient's enrolment at the request of the patient or their personal consultee (as described in the relevant patient, personal consultee and nominated consultee information sheets, as well as in the relevant consent and declaration forms).
- Patients, their personal consultees and nominated consultees may elect to opt-out of having the patient's GP informed of their enrolment in the study.

10.2 Case Report Form

All data will be entered on a secure electronic database held at the University of Liverpool.

The information technology (IT) infrastructure and will be supplied by the University of Liverpool and the Royal Liverpool University Hospital.

10.3 Record Retention and Archiving:

During the course of research, all records are the responsibility of the Chief Investigator. When the research trial is complete the records will be kept for a further 10 years (a requirement of the Research Governance Framework and Health Board Policy).

10.4 Compliance:

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

10.5 Clinical Governance Issues

The study may be selected for audit by any method listed below:

- The project may be identified via the risk assessment process.
- An individual investigator or department may request an audit.
- A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
- Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
- Projects may be randomly selected for audit by an external organisation.
- Internal audits will be conducted by a sponsor's representative

10.6 Non-Compliance

Non-compliances may be captured from a variety of different sources including CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

11. Finance and Publication Policy

11.1 Finance

Funding will be sought from :

- NIHR
- Departmental resources
- The funder has no involvement in the protocol or design of the study.
- The results will remain intellectual property of the research team.

11.2 Publication policy

It is planned to publish the trial results, in mutual agreement with the investigator team, in a scientific journal and at international congresses. Publication of the results of the trial as a whole is intended. Requirements for authorship will follow AMA guidelines. Any publication will take account of the International Committee of Medical Journal Editors (ICMJE).

The study will also be registered in a public register in accordance with the recommendations of the ICMJE. Any published data will observe data protection legislation covering the trial subject and investigators. Success rates or individual findings at individual trial sites are known only to the responsible institution.

Publications or lectures on the findings of the present clinical trial either as a whole or at individual investigation sites must be approved by the PI in advance, and the responsible institution reserves the right to review and comment on such documentation before publication.

13. Appendices

Appendix 1: Analysis of HRV variables

Parameter	Units	Description	Normal range
SDNN	ms	Standard deviation of the NN intervals	**101.19**
SDANN	ms	Standard deviation of average NN intervals	**41.47**
pNN50	%	Percentage of successive RR intervals that differ by more than 50ms	**18.80**
RMSSD	ms	Root mean square of successive RR interval differences	**0.08**
LF power	ms^2	Absolute power of the low frequency band (0.04 – 0.15Hz)	**2534.91**
HF power	ms^2	Absolute power of the high frequency band (0.15 – 0.4Hz)	**2592.32**
VLF power	ms^2	Absolute power of the very low frequency band (0.033 – 0.04Hz)	**8307.38**
LF/HF ratio	%	Ration of LF to HF power	**128.78**
SD1	ms	Poincre plot standard deviation perpendicular to the line of identity	**57.01**
SD2	ms	Poincre plot standard deviation along the line of identity	**134.13**
SD1/SD2 ratio	%	Ratio of SD1 to SD2	**2.49**

Appendix 2 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	Report to sponsor within 24 hours of learning of the event Report to the MREC within 15 days of learning of the event	SAE report form for non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the sponsor and MREC immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual progress report form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of study declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the research	No standard format However, the following Information should be included: Where the study has met	Main REC with a copy to be sent to the sponsor

			its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	

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