CLINICAL INVESTIGATION PLAN (CIP)
EN ISO 14155
Klinischer Prüfplan (MPG §40.3)

Heartrate variability during mechanical pressure support ventilation – comparing conventional and variable pressure support ventilation: a cross-over trial

Confidentiality Statement

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Device Name and Manufacturer	Infinity Delta Monitor, Dräger, Lübeck, Germany Evita Infinity V500, Dräger, Lübeck, Germany
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1. SPONSORS, INVESTIGATORS, MONITOR AND SIGNATURE

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2. SYNOPSIS OF THE CLINICAL INVESTIGATION

TITLE	Heartrate variability during mechanical pressure support ventilation – comparing conventional and variable pressure support ventilation: a cross-over trial					
ACRONYM	Heartrate variability during variable pressure support mechanical ventilation					
NAME OF DEVICE	Infinity Delta Monitor, Dräger, Lübeck, Germany Evita Infinity V500, Dräger, Lübeck, Germany					
DESCRIPTION OF THE PROCEDURES	Retrospectively determine heart rate variability from a standard electrocardiogram (Infinity Delta Monitor) recorded during conventional and variable pressure support mechanical ventilation (Evita Infinity V500). We hypothesize that heartrate variability (median of high frequency components over one hour) will increase during variable pressure support mechanical ventilation as compared to the conventional mode of mechanical ventilation.					
OBJECTIVES	Primary study objective: To compare the High frequency components (HF) of Heart Rate Variability (median over one hour measurement per patient) between conventional and variable pressure support ventilation. Secondary study objectives: Comparison of applicated tidal volumes and in heart rate variability parameters (median of standard deviation of R to R intervals (SDNN), median of high frequency to low frequency ratio over one hour measurement per patient) between conventional and variable pressure support ventilation. Exploratory objectives: Comparison of change in physiological parameters (e.g. systolic and diastolic arterial blood pressure, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide) between conventional and variable pressure support ventilation.					
TYPE OF THE INVESTIGATION	Interventional MPG § 40.3 cross-over trial					
PERIOD OF ENROLMENT	**First patient** **First visit**	*1Q*	**Last patient** **First visit**	*3Q*	**Last patient** **Last visit**	*3Q*
CENTER(S) / COUNTRY(IES)	*1 center (Medical University of Vienna), Austria*					
PATIENTS / GROUPS	*60 patients*					

INCLUSION CRITERIA	*patients undergoing therapy at an ICU* *patients aged between 18 and 80 years* *patients intubated and ventilated using SPN-CPAP/PS ventilator mode* *patients with sinus rhythm in electrocardiogram*
EXCLUSION CRITERIA	*patients aged < 18 or > 80 years* *patients with active heart pace maker / defibrillator* *patients with absent sinus rhythm in electrocardiogram* *patients with known severe disease of autonomous nervous system* *women, who are already known to be pregnant before taking part in this study*
COMPARATIVE DEVICE	*None.*
CONCOMITANT MEDICATION/CON-COMITANT DEVICE	*Every therapy / medication / monitoring is allowed as indicated per routine.*
EFFICACY ENDPOINTS	Primary study endpoint: High frequency components (HF) of Heart Rate Variability (median over one hour measurement per patient) Secondary study endpoints: Applicated tidal volumes and other heart rate variability parameters (standard deviation of R to R intervals (SDNN), high frequency to low frequency ratio), Exploratory endpoints: physiological parameters (systolic and diastolic arterial blood pressure, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide).
TOLERABILITY / SAFETY ENDPOINTS	*The occurrence of adverse events will be documented.*
QUALITY OF LIFE	*No quality of life parameters will be measured.*
STATISTICAL METHODOLOGY	**Primary Endpoint** High frequency components (HF) of Heart Rate Variability (median over one hour measurement per patient)

Secondary Endpoints

Applicated tidal volumes and other heart rate variability parameters (median of standard deviation of R to R intervals (SDNN) or high frequency to low frequency ratio over one hour measurement per patient)

Exploratory Endpoints

Physiological parameters (systolic and diastolic arterial blood pressure, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide).

Null and alternative hypotheses:

Null hypothesis of primary endpoint: there is no difference in the mean heartrate variability (measured as median high frequency components HF over one hour measurement per patient) between variable/noisy pressure support mechanical ventilation compared to conventional pressure support mechanical ventilation.

Alternative hypothesis of primary endpoint: there is a difference in the mean heartrate variability (measured as median high frequency components HF over a one hour measurement per patient) between variable/noisy pressure support mechanical ventilation compared to conventional pressure support mechanical ventilation.

Type-I and -II errors – power

The significance level was set to 0.05. The study was planned to achieve 80% power.

Interim analysis

No interim analysis.

Statistical methodology:

The primary endpoint will be analysed using ANOVA for repeated measurements accounting for group of pressure support mechanical ventilation as well as randomization order, the interaction between group and randomization order as well as gender and age.

Sample size calculation:

The study was planned based on preliminary data. When the sample size is 52, a single group t-test with a 0.05 two-sided significance level will have 80% power to detect the difference between a mean heartrate variability of 49 ms^2 in the conventional group and an mean

	of 59 ms^2 with variable pressure support mechanical ventilation assuming that the standard deviation of the difference is 25 ms^2. *Due to possible Drop-outs the sample size was set to 60 patients.*
STUDY EXTENSION	*If collection of data cannot be done in the given time.*

3. LIST OF ABBREVIATIONS

EOS	End of study
HF	High frequency components of heart rate variability
HRV	Heart rate variability
ICT	Interventional clinical trial
ICU	Intensive care unit
IEC	Independent ethics committee
LF	Low frequency components of heart rate variability
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
P_{max}	Maximum pressure support
P_{supp}	Mean support pressure
PSV	Pressure support ventilation
SOP	standard operation procedures
SDNN	standard deviation of R to R intervals of heart rate variability
SPN-CPAP/PS	Spontaneous continuous positive airway pressure/ pressure support
VPSMV	Variable pressure support mechanical ventilation

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TABLE 1. VISIT AND ASSESSMENT SCHEDULE

Day 1

1. Inclusion 2. Randomisation 3. Intervention A-B or B-A[1]

[1] A-B = conventional PSV – variable PSV, B-A = variable PSV – conventional PSV

5. INTRODUCTION

5.1 Background information

Spontaneous-continuous positive airway pressure support (SPN-CPAP/PS) is the routine ventilator mode used in critically ill patients submitted to an intensive care unit (ICU). It guarantees a positive end expiratory pressure, which prevents atelectasis and minimizes weaning time, by supporting the patient's respiratory drive.

A few years ago, this very established ventilation technique was modified by simply altering the rhythm and volume of gas application: instead of administering same tidal volumes in equal time intervals a variation of applied volume as well as altering frequency in ventilation is introduced. This ventilation method is termed noisy pressure support ventilation (noisy PSV) or variable pressure support ventilation (variable PSV). The variation of pressure support will be within a range around a mean support-pressure (P_{supp}) and won't exceed a maximum pressure (P_{max}), which are both adjusted before starting noisy PSV.

Any variation of breathing is physiological and may occur during speaking, moving and many other factors. As novel concept, we propose that such variation of ventilation rhythm and volume may have an important impact on heart rate variability (HRV), which is known as to be an indicator of a healthy heart (Wenckebach, 1914). Since Wolff et al. observed that HRV is an important predictor of mortality in coronary care units, investigation of HRV became more important (Wolf et al., 1978). Thayer and Lane recently found that low HRV is associated with an increasing mortality and proposed low HRV to be a marker for critical illness (Thayer et al., 2010, Thayer and Lane, 2007).

The analysis and further investigation of HRV has therefore become an important issue in modern medicine. Mechanical ventilation plays a pivotal role in ICUs and should be further improved. Mechanical ventilation per se is stressful for the cardiovascular system. Cardiovascular homeostasis is of major importance and we hypothesise that noisy PSV will decrease the stress applied to the human heart measured via heart rate variability (Zipes, 2004, Kleiger et al., 1987, Fozzard).

5.2 Rationale of clinical investigation

In this interventional clinical study, we will apply, in a randomized fashion, conventional PSV and variable PSV each for a duration of one hour. During ventilation we will record all data of the patients monitor, including the electrocardiogram (ECG), which is routinely monitored in our patients, and respiratory data, to determine HRV parameters retrospectively. All other ventilatory, hemodynamic and pharmacological treatment will be part of the clinical routine. As two modes of ventilation will be compared, this study is an interventional clinical cross-over trial.

Primary study objective:

To compare the high frequency components (HF) of Heart Rate Variability (median over one hour measurement per patient) from ECG data between conventional and variable pressure support ventilation.

The following parameters will be measured and calculated:

- ECG waveform at 200 Hz
- Pulse pressure waveform as part of the clinical routine
- Arterial blood gas analysis at the beginning and end of each ventilation mode
    - Arterial partial pressure of oxygen (PaO_2)

- Arterial partial pressure of carbon dioxide ($PaCO_2$)
- Arterial pressure waveform if part of the clinical routine
- All respirator data

6. OBJECTIVES OF THE CLINICAL INVESTIGATION (HYPOTHESIS)

6.1 Primary Objective (Hypothesis)

Primary endpoint is the High frequency component (HF) of the heart rate variability. For each patient a median of the HF-curve over one hour treatment will be calculated. This value is chosen, since the median of high frequency components is stable to measurement related artefacts.

Null hypothesis of primary endpoint:

There is no difference in the mean heartrate variability (median high frequency components HF over a one hour measurement per patient) between variable/noisy pressure support mechanical ventilation compared to conventional pressure support mechanical ventilation.

6.2 Secondary Objectives (Hypothesis)

Comparison of applicated tidal volumes and other heart rate variability parameters (median standard deviation of R to R intervals (SDNN) and median high frequency to low frequency ratio over one hour measurement per patients) between conventional and variable pressure support ventilation. Note that also for the secondary parameters, the median over a one hour continuous measurement per patient will be used for statistical analyses.

6.3 Exploratory Objectives

Comparison of change in Physiological parameters (systolic and diastolic arterial blood pressure, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide) between conventional and variable pressure support ventilation. In contrast to the primary and secondary parameters, the exploratory parameters are not measured during the whole study duration (one hour per treatment) but at the beginning and end of each treatment.

7. DESIGN OF THE CLINICAL INVESTIGATION

7.1 Population

This study is an interventional cross-over trial in N=60 patients.

7.1.1 Subject population

The study will include subjects between 18-80 years undergoing therapy at an anesthesiological ICU (ICUs: 9D, 13B1, 13C2). No absent sinus rhythm and no active implanted pacemaker or defibrillator is allowed. Participants will be informed and sign the written informed consent form after extubation and improvement of clinical condition.

7.1.2 Inclusion criteria

- patients undergoing therapy at an ICU
- patients aged between 18 and 80 years
- patients intubated and ventilated on SPN-CPAP/PS mode
- patients with sinus rhythm in electrocardiogram

7.1.3 Exclusion criteria

- patients aged under 18 or over 80 years
- patients with active heart pacemaker/defibrillator
- patients with absent sinus rhythm in ECG
- patients with severe autonomous nervous system disease
- women, who are already known to be pregnant before taking part in this study

7.2 POINT OF ENROLMENT

The subjects will be recruited on ICUs from the Department of Anaesthesia, General Intensive Care and Pain Management. The study will be performed in accordance with the Declaration of Helsinki (1964), including current revisions and the study protocol will be submitted to the Ethics Committee of the Medical University of Vienna for approval. The subject's consent will be collected after extubation and clinical improvement, as far as possible regarding the patient's state of health. All subject names will be kept confidential in the investigators files. Subjects will be identified throughout documentation and evaluation by the number allotted to them during the study. The subjects will be informed that all study findings will be stored and handled in strictest confidence. A data protocol in case report form will be used.

7.2.1 Females of childbearing age

Females of childbearing age will be included.

7.2.2 Duration of the clinical investigation

The duration of the clinical cross-over trial is one year. First, subjects will be included in the clinical study according to inclusion and exclusion criteria. The order of the two interventions will be randomized. According to the randomization, subjects will be allocated first to conventional PSV (duration one hour) then to variable PSV (one hour) or vice versa. Thereafter, the study observation period will be over. Subjects will not have to come to follow up visits or investigations.

7.3 Withdrawal and replacement of subjects

7.3.1 Criteria for withdrawal

Discontinuation from the study is to be understood when the subject did not undergo the end of study (EOS) examination and/or all pivotal assessments during the clinical investigation.

Subjects must be withdrawn under the following circumstances:

- at their own request
- if the investigator feels it would not be in the best interest of the subject to continue
- if the subject violates conditions laid out in the consent form / information sheet or disregards instructions by the clinical investigation personal

- in case of severe medical emergency (e.g. cardiac arrest, reanimation)

In all cases, the reason why subjects are withdrawn must be recorded in detail in the case record file (CRF) and in the subject's medical records. Should the clinical investigation be discontinued prematurely, all clinical investigation materials (complete, partially completed and empty CRFs) will be retained.

7.3.2 Follow-up of patients withdrawn from the clinical investigation

In case of premature discontinuation, no follow-up will be performed. Replacement policy

Patients excluded from the study for any of the reasons above will be replaced.

7.4 Premature termination of the clinical investigation

The sponsor has the right to close this clinical investigation at any time. The internal ethical committee (IEC) and the competent regulatory authority must be informed.

8. METHODOLOGY

The study will be performed for the time of HRV measurement (one hour conventional PSV followed by one hour variable PSV, in total two hours without interruption, randomized fashion).

8.1 Treatment duration and modification

Patients will be screened for eligibility before ventilation-mode switch according to inclusion and exclusion criteria.

8.2 Medical Devices

All devices used in the present cross-over trial are part of the clinical routine (Evita Infinity V500 and Infinity Delta). No extra medical device will be used. Both ECG recording and classical as well as variable PSV ventilator modes are used in routine clinical ICU therapy.

8.2.1 Manufacturer (Model or Type Number including software and accessories): Storage Instructions:

Manufacturer: Dräger, Model: Evita Infinity V500, Serial Number: Clinical routine ventilation on ICU

Manufacturer: Dräger, Model: Infinity Delta, Serial Number: Clinical routine monitoring on ICU

8.2.2 Installation and handling instructions

According to clinical routine instructions.

8.2.3 Intended use

According to clinical routine instructions.

8.2.4 In-/Decrease of the treatment frequency

Not applicable.

8.2.5 Interruption of the treatment

The treatment will be interrupted in case of technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest and cardiopulmonary reanimation.

8.2.6 Premature permanent discontinuation of the treatment

Premature discontinuation of the cross-over trial is not planned. There are no interim analyses.

8.2.7 Premature permanent discontinuation due to an adverse event

Not applicable.

8.2.8 Premature permanent discontinuation due to another reason than adverse event

Not applicable.

8.2.9 Procedures for subjects' compliance

All recordings will be performed by the investigators.

8.2.10 Concomitant medication

All concomitant medications are allowed.

8.2.11 Interactions, reverse reactions and side effect of the medical device:

Not applicable. All devices used are part of the clinical routine ICU therapy. Both the conventional and variable PSV modes are part of the clinical routine ICU therapy. The arterial blood gas analyses are not part of the clinical routine ICU therapy. Potential risks and side effects of taking arterial blood gas analyses include infection and bleeding only in case of inappropriate usage.

8.3 Randomization and stratification:

Subjects will be randomized to the order of conventional and variable PSV treatment (first conventional PSV and then variable PSV or first variable PSV and then conventional PSV). The randomization will be performed by block-randomization using the online randomization program of the Medical University of Vienna (https://www.meduniwien.ac.at/randomizer/web/login.php). There will be no stratification of subjects studied. Only the statistician (Dr. Graf) and the responsible person performing measurements (Mr. Schnetzinger) will have access to the online randomization program.

8.4 Blinding

No blinding procedure will be performed. The patient will be blinded, with respect to the respiratory-treatment, due his medical status.

8.4.1 Emergency procedure for unblinding

Not applicable.

8.4.2 Unblinding-procedure at the end of the clinical investigation.

Not applicable.

8.5 Benefit and risk assessment

Both the Infinity Delta Monitor and the Evita Infinity V500 are part of the clinical routine ICU therapy. Also, the ventilator mode conventional PSV and variable PSV are part of the clinical routine ICU therapy. The only procedures performed in the present cross-over trial is that the ventilator mode will be changed from conventional PSV to variable PSV or vice versa. Therefore, there are no actual risks for the patients during the present study or clinical ICU routine therapy. The only additional procedures attributed to this study is that extra arterial blood gas measurements will be performed during the study. These risks are low, as the person performing the study will be trained in taking arterial blood gas analysis and such procedures are taken also routinely during ICU stay.

8.6 Clinical investigation procedures

8.6.1 General rules for clinical investigation procedures

- All investigation measures have to be documented with date (dd.mm.yyyy).

- The dates of all procedures should be according to the clinical investigation plan (CIP). The time margins mentioned in the clinical investigation flow chart are admissible. If, for any reason, a clinical investigation procedure is not performed within scheduled margins a CIP deviation should be noted, and the procedure should be performed as soon as possible or as adequate.

8.6.2 Screening investigation

All patients scheduled for ICU will be screened. Eligible patients will be included in the study. Informed patient consent will be taken after the patients have been extubated and transferred to the normal ward.

8.6.3 Treatment

The treatment includes setting the ventilator to conventional PSV mode for one hour and variable PSV mode for one hour (in total 2 hours of treatment per patient, randomized fashion). Arterial blood gases taken at the beginning and the end of each ventilator mode (2x per mode, in total 4 arterial blood gases per patients) will be taken in addition to the clinical routine therapy. Thereafter, the treatment will be terminated and no patient follow up will be performed.

8.6.4 Laboratory Tests

Blood gas analysis will be taken at the beginning and the end of each treatment (2 times 2 arterial blood gas analyses, in total 4 blood gas analyses per patient).

8.6.5 End-of-clinical investigation (EOI) examination

No end-of-clinical-investigation (EOI) examination will be performed.

9. SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse events (AEs)/Adverse device effects (ADEs)

9.1.1 Summary of known and potential risks of the medical device

Both the Infinity Delta Monitor and the Evita Infinity V500 are part of the clinical routine ICU therapy. These devices are licensed for the clinical usage and will be used only for their specific purpose. Therefore, there are no extra risks associated with this clinical study. Theoretical risks include failure of the device with harm to the patients. In case of technological failure of the devices the subject may be harmed as monitoring of vital parameters (Infinity Delta Monitor) or mechanical ventilation (Evita Infinity V500) might be inadequate, injurious or in theory lethal.

9.1.2 Definition of adverse event and adverse device effect

Adverse events (AEs) are any significant hemodynamic or respiratory impairment (e.g. in- or decrease of systolic or diastolic arterial blood pressure or heart rate or parameters of respiration of < or >30% baseline). Further, any technological problems are defined adverse device effects (ADEs). Such impairments are not expected during the present study.

9.2 Serious adverse events (SAE)/Serious adverse device effects (SADEs)

Serious adverse events (SAEs) are hemodynamic or respiratory impairments (see AEs) that are potentially life-threatening to the subject. Serious adverse device effects (ADEs) are technological problems that are potentially life-threatening to the subject.

9.2.1 Hospitalization – Prolongation of existing hospitalization

Not applicable.

9.2.2 SAEs /sADE related to study-mandated procedures

Not applicable.

9.2.3 Pregnancy

Women, who are known to be pregnant before taking part in the study, are excluded.

9.3 Severity of adverse events/adverse device effects

Not applicable.

9.4 Relationship to medical device

There is no financial or other relationship between the authors/investigators and the manufacturer of the medical devices used.

9.5 Reporting procedures

AEs or ADEs will be reported within one week to the ethical care committee.

9.5.1 Reporting procedures for SAEs/SADEs

SAEs and SADEs will be reported within 24 hours to the ethical care committee and the study will be paused until clarity about the SAEs/SADEs reason.

10. FOLLOW-UP

10.1 Follow-up of clinical investigation participants including follow-up of adverse events

No follow-up of clinical investigation participants will be performed.

10.2 Treatment after end of clinical investigation

The clinical investigation has no effect on the treatment of the patient especially not after its end.

11. STATISTICAL METHODOLOGY AND ANALYSIS

11.1 Analysis sets

The study will be analyzed using the per-protocol set. This analysis set comprises all subjects who underwent treatment with both pressure support systems and did not violate the protocol in a way that might affect the evaluation of the primary study parameter. Drop-outs may occur if the treatment will be interrupted in case of technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest and cardiopulmonary reanimation. In case of a drop-out, the evaluation of the primary parameter is not meaningful so that drop-outs will be excluded from the analysis. All treatment interruptions will be documented and summarized.

Violations of the protocol due to a wrong randomization ordering (reverse than randomized) are less likely because measurements are done by one person (Mr. Schnetzinger) who is also the holder of the randomization list.

11.2 Sample size considerations

A sample size calculation has been carried out. Basis for this sample size calculation is preliminary data for the primary endpoint, the high frequency components of heart rate variability (median over one hour measurement per patient, further on denoted as HF). We assume a mean HF of about 49 ms^2 for the conventional mode of mechanical ventilation. An increase of on average 10 ms^2 (to 59 ms^2) for the variable pressure support mechanical ventilation is assumed. For sample size calculation, the standard deviation of the difference was set to 25 ms^2.

When the sample size is 52, a single group t-test with a 0.05 two-sided significance level will have 80% power to detect the assumed effect.

Empirical knowledge of eventual intervention-related drop-out of patients from the study, leads to a sample size of 60 patients. (drop outs due to technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest and cardiopulmonary reanimation).

11.3 Relevant protocol deviations

Protocol deviations may occur if the treatment will be interrupted in case of technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest and cardiopulmonary reanimation. In case of a drop-out, the evaluation of the primary parameter is not meaningful, so that drop-outs will be excluded from the statistical analysis.

11.4 Statistical analysis plan

see 11.6

11.5 Missing, unused and spurious data

Missing, unused or spurious data due technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest and cardiopulmonary reanimation will be reported and presented. Records with missing data will be excluded from the analysis.

11.6 Endpoints analysis

11.6.1 Primary endpoint analysis

The median of the high frequency components (HF) measured over one hour per patient will be described descriptively separately for the two pressure support mechanical ventilation groups using means, standard deviations as well as medians and quantiles. Graphical illustration will be performed using boxplots.

To compare the mean HF between conventional and variable pressure support mechanical ventilation, first a paired t-test will be performed.

Furthermore, an ANOVA for repeated measurements, accounting for group (conventional vs. variable), randomization order, the interaction between group and randomization order as well as other influence factors (as gender and age) will be performed.

The significance level for the primary analysis is set to 0.05.

11.6.2 Secondary endpoint analysis

Similar to the main outcome parameters the median of the standard deviation of normal to normal (SDNN) and the median of high-frequency-low-frequency-ratios (HF-LF-ratio) over one hour measurements will be described descriptively with boxplots as well as means, standard deviations, medians and quantiles.

Furthermore, mean SDNN and HF-LF-ratio will be compared between treatment groups using paired t-tests. In addition, an ANOVA for repeated measurements, accounting for group, randomization order, the interaction between group and randomization order as well as other influence factors (as gender and age) will be performed.

The significance level for the secondary analyses is set to 0.05.

11.6.3 Safety and tolerability endpoints

The occurrence of adverse events will be described descriptively by frequencies and percentages.

11.6.4 Exploratory analyses

All exploratory parameters, which are obtained from arterial blood gas analysis (systolic and diastolic arterial blood pressure, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide) will be described with descriptive statistics (boxplots, means, standard deviations, medians and quartiles) separately for the two groups.

11.7 Interim analysis

No interim analysis is planned.

Criteria for the termination of the clinical investigation:

Not applicable as no interim analysis planned.

11.8 Software program(s)

Statistical evaluation will be performed using SPSS and R.

12. DOCUMENTATION AND DATA MANAGEMENT

12.1 Documentation of study results

A subject screening and enrollment Log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

12.1.1 Case Report Form (CRF)

For each subject enrolled, regardless of medical device initiation, a “Paper-CRF” must be completed and signed by the principal investigator or co-investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis. CRF entries and corrections will only be performed by study site staff and authorized by the investigator. In a “Paper-CRF” all forms should be completed using a pen and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator, co-investigator or study nurse. The entries will be checked by trained personnel (Monitor) and any errors or inconsistencies will be checked immediately. The monitor will collect original completed and signed CRFs at the end of the study. A copy of the completed and signed CRFs will remain on site. The original “Paper-CRFs” will be passed to Maximilian Schnetzinger. He is the data manager.

12.1.2 Data Collection

Data collected at all visits are entered into an interactive form. The CRFs will be source documents verified following guidelines established before study onset as detailed in the Monitoring Plan. Maintenance of the study database will be performed by Maximilian Schnetzinger.

12.1.3 Identification data to be considered as source data

Not applicable.

12.2 Safekeeping

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file, and subject clinical source documents. The investigator's file will contain the CIP/amendments, IB/Manual for Medical Device, CRFs (eCRF

printout), standard operation procedures (SOPs), data clarification and query forms, EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per EUROPENAN Standard of EN ISO 14155 (incl. GCP) and local regulations.

Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc. These two categories of documents must be kept on file by the investigator for as long as needed to comply with national and international regulations (in Austria 15 years after discontinuing clinical development or after the last marketing approval). If source documents are not durable as long as needed (e.g. ECG printouts) they must be preserved as a copy. No study document should be destroyed without prior written approval. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

12.3 Quality Control and Quality Assurance

Datasets will be controlled weekly by all members of the team.

12.3.1 Periodic Monitoring

The monitor will contact and visit the investigator regularly and will be allowed, on request, to have access to all source documents needed to verify the entries in the CRFs and other CIP-related documents provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the CIP and the completeness, consistency and accuracy of the data being entered on them. The monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs/SADEs and the recording of the main efficacy, safety, and tolerability endpoints. To be ISO 14155 compliant at least 3 monitoring visits are scheduled. An initiation visit, one routine visit and a final visit (3 visits in total) after the last patient, had finished the study. The monitor will be working according to SOPs and will provide an ISO 14155-compliant monitoring report after each visit for the sponsor and the investigator.

12.3.2 Audits and Inspections

Upon request, the investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to regulatory authority inspectors. The main purpose of an audit or inspection is to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

12.4 Reporting and Publication

12.4.1 Final Report

Within one year after the final completion of the study, a full report will be written. The principal Investigator will be asked to review and sign the final report.

12.4.2 Publication of Study Results

The findings of this study will be used to design prospective trials using HRV in the perioperative setting.

13. ETHICAL AND LEGAL ASPECTS

13.1 Informed Consent of Subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical investigation, the patient must give written consent to participation in the study. During the instruction, the patients are to be made aware of the fact that they can with-draw their consent - without giving reasons – at any time without their further medical care being influenced in any way. In addition to the comprehensive instructions given to the patients by the investigator, the patients also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress. The patients must agree to the possibility of study-related data being passed on to relevant authorities. The patients must be informed in detail of their obligations in relation to the patient insurance in order not to jeopardize insurance cover.

13.2 Acknowledgement/approval of the Clinical Investigation

The investigator (or a designated CRO) will submit this CIP and any related document provided to the subject (such as subject information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the clinical investigation, and should be documented in a dated letter to the investigator. Serious Adverse Events /Serious Adverse Device Effects have to be reported to the ethics committee and to the Austrian Agency for health and Food Safety (AGES). Adverse events / Adverse device effects- whether serious and/or unexpected, and possibly endangering the safety of the study participants are likewise to be reported to the ethics committee. The clinical investigation shall be performed in full compliance with the valid legal regulations according to the Medical Device Law (MPG Medizinproduktegesetz as actual amendment) of the Republic of Austria and the ISO 14155 (as actual amended). The study must be notified to the Austrian Agency for Health and Food Safety (AGES) and Ethics Committee.

13.2.1 Changes in the Conduct of the Clinical Investigation Plan

Amendments of the clinical investigation plan

Proposed amendments must be submitted to the appropriate CA and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Termination of the clinical investigation

If the sponsor or the investigator decides to terminate the clinical investigation before it is completed, they will notify each other in writing stating the reasons of early termination. In terminating the study, the sponsor and the investigator will ensure the adequate consideration is given to the protection of the subject interests. The investigator, sponsor or designated CRO will notify the relevant regulatory authorities and EC. Documentation will be filed in the Trial Master (Clinical Investigation) clinical investigation and Investigator Files.

13.3 Insurance

During their participation in the clinical investigation the patients will be insured as defined by legal requirements. The principal investigator of the clinical investigation will receive a copy of the insurance conditions of the *patient's insurance*. The sponsor is providing insurance in order to indemnify (legal and financial coverage) the investigator/centre against claims arising from the clinical investigation, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of clinical investigation-related injuries will comply with the applicable regulations. Details

on the existing patient's insurance are given in the patient information sheet and will be filed subsequently.

13.4 Confidentiality

The information contained in this document, especially unpublished data, is the property of the Department of Anaesthesia, General Intensive Care and Pain Management, Medical University Vienna. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from Department of Anaesthesia, General Intensive Care and Pain Management, Medical University Vienna, except to the extent necessary to obtain informed consent from those persons to whom the medical device may be treated with.

13.5 Ethics and Legal Requirements

13.5.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 56th WMA General Assembly, Tokyo, Japan, 2008).

13.5.2 Good Clinical Practice (EN ISO 14155)

ISO 14155 addresses good clinical practices for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety and performance of medical devices for regulatory purposes.

It specifies general requirements intended to:

- protect the rights, safety and well-being of human subjects,
- ensure the scientific conduct of the clinical investigation and the credibility of the clinical
    - investigation results,
- assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other
    - bodies involved in the conformity assessment of medical devices

The principal investigator of the clinical investigation shall guarantee that only appropriately trained personnel will be involved in this. All clinical investigations must follow the EUROPENAN Standard of EN ISO 14155 and, if applicable, the Code of Federal Regulations (USA). In other countries in which EN ISO Guidelines exist, the investigators will strictly ensure adherence to the stated provisions. Therefore, this study follows the EN ISO Guidelines embedded in the Austrian medical device act.

14. ACKNOWLEDGEMENTS

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