CLINICAL INVESTIGATION PLAN

(according to DIN EN ISO 14155:2012-01)

ASSESSMENT OF THE CAPABILITY OF PULMOVISTA 500 TO CONTINUOUSLY MONITOR CHANGES OF VENTILATION OVER TIME.

„PulmoVista 500"

Multicenter, prospective, non-interventional, open trial

Version 1.0F, 21.11.2016

Autors: Associate Professor (USA) Dr. med. Oliver C. Radke
Felix Fischer, Mario Graf

Sponsor:
Drägerwerk AG & Co. KGaA
Moislinger Alle 53-55
23558 Lübeck, Germany

CIP Code: PV500

Coordinating Investigator:
PD Dr. med. Peter Spieth

Confidentiality

Investigator

We, the undersigned, agree to conduct this study according to the above protocol. We commit our-selves to treat, to follow-up, and to document all included participants according to the study protocol.

_____	_____
Name	Date, Signature
_____	_____
Name	Date, Signature
_____	_____
Name	Date, Signature

TABLE OF CONTENTS

TABLE OF ABBREVATIONS

AE	*adverse event*
ADE	*adverse device effect*
ALI	*acute lung injury*
BfArM	*federal authority (dt.:Bundesinstitut für Arzneimittel und Medizinprodukte)*
CCF	*cross-correlation function*
CPAP	*Continuous Positive Airway Pressure*
CT	*computed tomography*
DLT	*double lumen tube*
(e)CRF	(*electronic) case report form*
EIT	*electrical impedance tomography*
FPFV	*first patient first visit*
GCP	*good clinical practice*
ICD	*implantable cardioverter defibrillator*
ICH	*International Counsil on Harmonization*
ICU	*Intensive Care unit*
IfU	*Instructions for Use*
ITT	*Intent To Treat*
ISF	*investigator site file*
KKS	*Coordination Centre for Clinical Trials*
LPLV	*last patient last visit*
MPG	*german medical device law*
MRI	*magnetic resonance imaging*
NA	*not applicable*
NaCl	*Sodium chloride*
ND	*not done*
OLV	*one lung ventilation*
PDA	*peridural anesthesia*
PEEP	*positive end-expiratory pressure*
SAE	*serious adverse event*
SADE	*serious adverse device effect*
SAS	*statistical analysis system*
SBT	*spontaneous breathing trial*
SDV	*source data verification*
SOP	*standard operating procedure*
SPSS	*statistical package for the social sciences*
TEA	*thoracic epidural anesthesia*
TMF	*trial master file*
USADE	*unanticipated serious adverse device effect*
VT	*tidal volume*

1 INTRODUCTION

1.1 INVOLVED PERSONS/INSTITUTIONS

Sponsor and manufacturer of the product:

Drägerwerk AG & Co. KGaA
represented by,
Dipl.-Ing. Felix Fischer
Moislinger Allee 53-55, 23558 Lübeck,
Germany
Phone: +49 451 882 2888
Fax: +49 451 882 72888

Coordinating Investigator:

PD Dr. med. Peter Spieth
Klinik und Poliklinik für Anästhesiologie
und Intensivtherapie
Universitätsklinikum Carl Gustav Carus
der Technischen Universität Dresden
Fetscherstraße 74, 01307 Dresden
Germany

Medical Advisor:

Associate Professor (USA) Dr. med. Oliver C. Radke
Klinik für Anästhesiologie und Operative Intensivmedizin
Klinikum Bremerhaven-Reinkenheide gGmbH
Postbrookstraße 103, 27574 Bremerhaven
Germany
Phone: +49 471 299 3268
Fax: +49 471 299 3268
E-Mail: oradke@pcat.de

Trial site 1:

Klinik und Poliklinik für Anästhesiologie und Intensivtherapie
Medizinischen Fakultät Carl Gustav Carus
der Technischen Universität Dresden
Fetscherstraße 74, 01307 Dresden
Germany

Trial site 2: Klinik für Anästhesiologie und Intensivmedizin
Medizinische Hochschule Hannover (MHH)
Carl-Neuberg-Str. 1, 30625 Hannover
Germany

Trial Management/Monitoring:
Mario Graf,
Koordinierungszentrum für Klinische Studien Dresden
der Medizinischen Fakultät Carl Gustav Carus
der Technischen Universität Dresden
Fetscherstraße 74, 01307 Dresden
Germany
Phone: +49 351 458-18622
Fax: +49 351 458-5799
E-Mail: mario.graf@uniklinikum-dresden.de

Data Management: Stephan Friedrich, KKS Dresden
Koordinierungszentrum für Klinische Studien Dresden
der Medizinische Fakultät Carl Gustav Carus
der Technischen Universität Dresden
Fetscherstraße 74, 01307 Dresden
Germany
Phone: 0351 458-14963
Fax: 0351 458-5799
E-Mail: stephan.friedrich@uniklinikum-dresden.de

Biostatisticians: Statistical Planning:
Prof. Dr. med. Michael Imhoff
Abteilung für Medizinische Informatik, Biometrie und Epidemiologie
Ruhr-Universität Bochum, 44780 Bochum
Home Office:
Buchenweg 18c-d, 23568 Lübeck
Germany
Phone: +49-451-707698-0
Fax: +49-451-707698-29
Mobile: +49-171-7411198
Email: mike@imhoff.de

Statistical Evaluation:
Uta Schwanebeck
Koordinierungszentrum für Klinische Studien Dresden
der Medizinischen Fakultät Carl Gustav Carus
der Technischen Universität Dresden
Fetscherstraße 74, 01307 Dresden
Germany
Phone: +49 351 458-15134
Fax: +49 351 458-5799
E-Mail: uta.schwanebeck@uniklinikum-dresden.de

1.2 SYNOPSIS

Title	Assessment of the capability of PulmoVista 500 to continuously monitor changes of ventilation over time.
Short Title	PulmoVista 500
Target population	Following patients will be enrolled: - Intensive care unit (ICU) patients, who are mechanically ventilated via an artificial airway (endotracheal tube or tracheostomy cannula) and who are expected to be subjected to major changes in their ventilator settings will be monitored with the PV500 device before, during and after the changes. These changes in the ventilator settings should result in recognizable changes in the distribution of ventilation in the lungs. Examples of such interventions are: • Spontaneous breathing trial (SBT) using the ventilator (as opposed to SBT using a T-piece) • Switching between different modes of ventilation (e.g. volume controlled, pressure controlled, pressure support, CPAP) • Initial adjustment of ventilation after ICU admission • Weaning from ventilation in preparation for extubation • PEEP trials and recruitment maneuvers • Suctioning maneuvers - Patients who are scheduled for surgeries that require blocking of one bronchus (e.g. one-lung-ventilation by insertion of a double lumen tube or bronchial blocker)
Trial design	Multicenter, prospective, non-interventional, open trial
Objectives of the Trial	<u>Primary objective</u> The capability of PulmoVista 500 to continuously

	monitor ventilation and its changes. Secondary Objective • To assess the capability of PulmoVista 500 to detect regional changes of ventilation and lung volume. • Documentation of any safety events related to the use of PulmoVista 500 • Assessing the use specific clinical helpfulness of PulmoVista 500
Endpoints of the Trial	Primary Endpoint The capability of PulmoVista 500 for continuous monitoring of ventilation and its changes at different points in time during varying states of regional ventilation, the cross-correlation function (CCF) between global tidal impedance (EIT) waveforms and global tidal volume (ventilator) curves will be evaluated. Secondary Endpoints - First secondary endpoint: To assess the capability of PulmoVista 500 to detect changes in regional ventilation by evaluating the cross correlation between impedance waveforms derived from PulmoVista 500 and volume curves derived from ventilator during one-lung-ventilation. - Assess that changes of tidal volumes induced by ventilator settings can be monitored by the "Trends view" (see chapter 23.2) - Assess that changes of the end-expiratory lung volumes (induced by e.g. PEEP changes, recruitment and suctioning maneuvers) can be monitored by "dEELI trend view" (see chapter 23.2) - Documentation of any safety events related to the use of PulmoVista 500 - Clinical helpfulness of PulmoVista 500 is proven if • see attachments (chapter 23.1) clinical usability
Sample Size	• 80 patients 25 patients shall be enrolled in a subgroup of patients with one-lung-ventilation (OLV)

Anticipated Duration	Relating to trial First patient first visit: January 2017 Last patient last visit: September 2017 Relating to patient: 8 hours (+Safety Follow-up)
Inclusion Criteria	• The population included in the clinical study will be selected from a pool of patients undergoing respiratory support who are scheduled to have their ventilation settings changed. As a subgroup, patients who are scheduled for surgeries that need one-lung-ventilation (OLV) will be enrolled to the study. • Male and female patients at the age of 18 years or older • On respiratory support in ICU care or scheduled for such (e.g. postoperatively) or scheduled for surgery with OLV • Patients of which the monitoring of ventilation distribution may be of clinical interest • Patients being ventilated via an artificial airway with a mechanical ventilator that is compatible with PulmoVista 500 • Patients scheduled for changes in ventilation settings that may cause relevant changes in the ventilation • Chest circumference between 70 and 150 cm • Written informed consent to participate in the study provided by either the patient or the legal representative of the patient.
Exclusion Criteria	• Currently has a permanent or temporary pacemaker, implantable cardiac device (ICD) or other device emitting electrical energy • a BMI ≥ 50 • tidal volume (VT) ≤ 200 mL • Current uncontrolled body movements such as tics, tremors or seizures, • Current wound dressings or infections on the chest that might interfere with the PulmoVista 500 electrode belt placement • Women of child bearing potential whose pregnancy cannot be excluded based on a pregnancy test or other proven facts.

	• Allergic to materials used in the electrode belt • Participation of the patient in an interventional trial within the last four weeks before enrollment in this trial • Evidence suggesting that the patient or his legal representative is not likely to follow the trial protocol (e.g. lacking compliance) • Known infectious diseases that require isolation of patient (e.g. MRSA) • Concomitant use of an air anti-decubitus medical mattress with dynamic inflation that cannot be deactivated during EIT measurements
Conduct of the trial	Visit 1 - Screening and Enrollment (Day (-2) - 0)) • Screening • Pregnancy Test or Exclusion • Check Inclusion and Exclusion Criteria • Informed Consent Process • Demography • Clinical Anamnesis • Medical History Visit 2 (Day 0) • EIT measure • Recording of EIT Data Visit 3 - Follow up (Day 1 - 3) • Check of adverse events General • Data of CT-, MRI-images, ultrasound assessments and radiographs not taken especially for this study, but due to necessary medical treatment taken during the period of day –2 to +3.
Trial related procedures and laboratory examinations	• Measurement with PulmoVista 500 during ventilation for a maximum period of eight hours • Pregnancy test if necessary
Investigational device	PulmoVista 500 is a non-invasive monitoring device used as an adjunctive diagnostic tool for assessing the distribution of ventilation in

Manufacturer:	patients undergoing respiratory support. Drägerwerk AG & Co. KGaA Moislinger Allee 53-55 23558 Lübeck, Germany

Table 1: Visit Schedule

scheduled for day	**Visit 1** **Screening and Enrollment** **(-2) or (-1) or 0**	**Visit 2** **Trial** **0**	**Visit 3** **Follow Up (safety)** **1 or 2 or 3**
Informed Consent	x		
Inclusion/Exclusion Criteria	x		
Demographics	x		
Medical/Treatment History	x		
Vital Signs	x	x	
Pregnancy Testing	x		
SAE administration		x	x

2 INVESTIGATIONAL DEVICE PULMOVISTA 500

2.1 SUMMARY DESCRIPTION AND PURPOSE

PulmoVista 500 is a lung function monitor for clinical use which continuously generates cross-sectional images of the lung function by applying the technique of electrical impedance tomography (EIT).

To perform bio-impedance measurements, an electrode belt containing 16 electrodes is placed around the chest wall. Additionally, one reference electrode must be attached to a central point to the body, preferably on the abdomen. The reference electrode ensures that all measurements at different electrode pairs are referenced to the same electric potential[1] .

PulmoVista 500 provides graphical information about the regional distribution of ventilation and changes of end-expiratory lung volume. The temporal resolution of this information allows observing specific conditions of different lung regions.

PulmoVista 500 is a CE released class IIa medical device manufactured by Drägerwerk AG & Co. KGaA, Lübeck Germany. It is distributed within Europe since April 2011.

2.2 DETAILS CONCERNING THE MANUFACTURER

Drägerwerk AG & Co. KGaA is an international company in the fields of medical and safety technology. Since 1889, Dräger has been developing technical devices and solutions for use in clinical, industrial or mining applications, in firefighting or rescue services.

2.3 MANUFACTURING OF PULMOVISTA 500 AND SUPPLY TO THE TRIAL SITES

The device PulmoVista 500 is produced by the Drägerwerk AG & Co. KGaA

Dräger provides one of the devices to each trial site as a loan device for the duration of the study.

2.4 DESCRIPTION OF THE INVESTIGATIONAL DEVICE

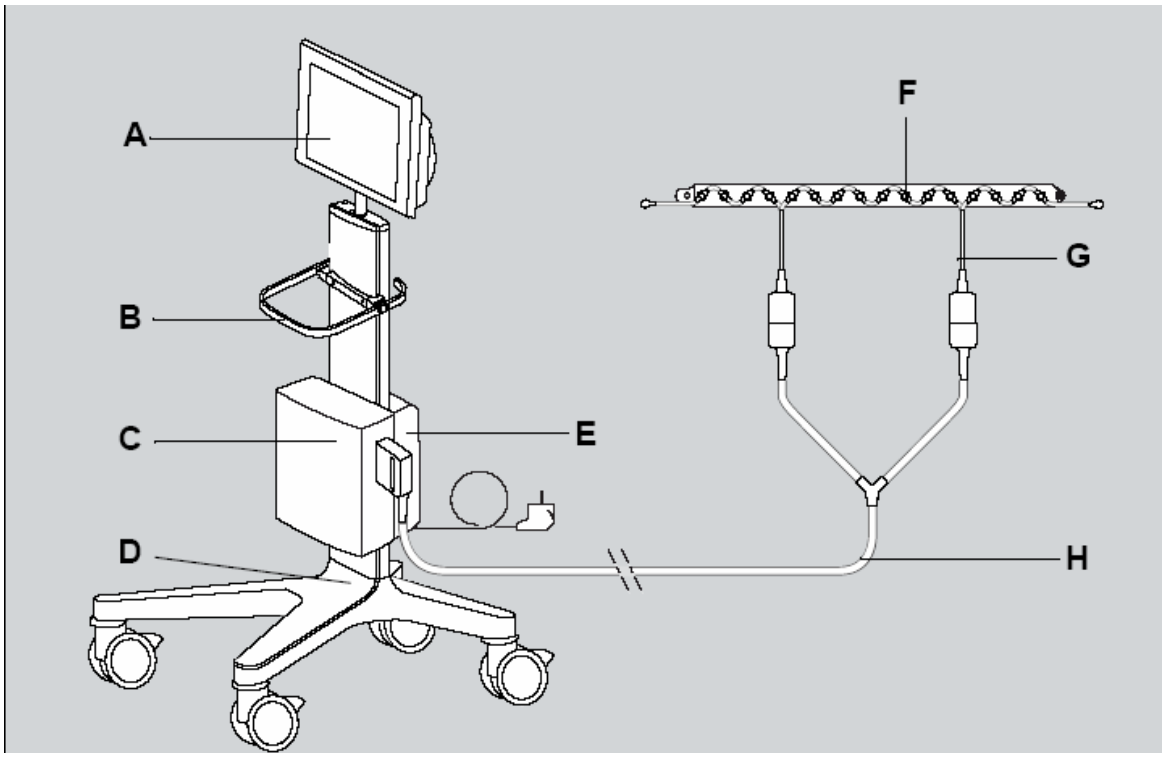
PulmoVista 500 is a non-invasive monitoring device used as an adjunctive diagnostic tool for assessing the distribution of ventilation. PulmoVista 500

[1] Teschner E, Imhoff M, Leonhardt S. Electrical Impedance Tomography: The realisation of regional ventilation monitoring. Drägerwerk AG & Co. KGaA 2015; Reference-Nbr 90 66 788; 19

allows visualization and evaluation of the lungs by applying the Electrical Impedance Tomography (EIT) technique.

PulmoVista 500 continuously determines the regional bioimpedance of the tissue within one cross-sectional plane (the so-called "electrode plane") of the thorax. To perform the EIT measurements, an electrode belt (F) containing 16 electrodes has to be placed around the chest wall of the patient and must be connected to PulmoVista 500 via a patient cable and a trunk cable (G, H). The electrode belt is made of silicone rubber, whereas the electrodes are made of conductive, carbonized silicone rubber. The electrode cables are made of different plastics (thermoplastic polyurethane (TPU), polyamide (PA), polyurethane (PUR), polypropylene (PP), thermoplastic elastomer (TPE), polybutylene terephthalate (PBT)). The impedance of lung tissue varies with the air content. Thus, ventilation distribution and changes of end-expiratory lung volume that occur within the electrode plane can be detected and displayed.

PulmoVista 500 is made up of the Infinity Medical Cockpit C500 (A), the Power Supply Unit P2500 (E) and the EIT module (C). Handle (B) and trolley (D) allow easy transport of PulmoVista 500 within the hospital.



Infinity Medical Cockpit C500 (A)

The Infinity Medical Cockpit provides the user interface of PulmoVista 500 in form of a standardized display and control unit that is also used in other Dräger products. The display software running on the Infinity Medical Cockpit

uses common standardized operating concepts applied for various Dräger products to facilitate ease of use for the clinicians.

Power Supply Unit P2500 (E)

The Power Supply Unit P2500 converts the AC mains supply voltage into a DC safety low voltage to power the EIT module as well as the Infinity Medical Cockpit. The Power Supply Unit is medical grade implementing all required safety measures for medical electrical equipment to protect patient, user and bystander.

EIT Module (C)

The EIT module is the signal processing front-end that generates the measurement currents and determines the resulting voltages at the chest electrodes.

The software version of PulmoVista 500 is named as *1.12*. Upgrades of this version will be possible and documented

Applied Standards in full or in part:	
EN ISO 14971: 2009 *(ISO 14971: 2007)*	Medical Devices - Application of Risk Management to Medical Devices
EN 60601-1: 2006 / AC: 2010 (*IEC 60601-1: 2005 / CORR 1: 2006 / CORR 2: 2007)* *(IEC 60601-1:1988/A1: 1991/ A2: 1995)*	Medical electrical equipment -- Part 1: General requirements for basic safety and essential performance
EN 60601-1-2: 2007 / AC: 2010 *(IEC 60601-1-2: 2007)* *(IEC 60601-1-2:2001/A1:2004)*	Medical electrical equipment Part 1-2: General requirements for safety – Collateral standard: Electromagnetic Compatibility - Requirements and tests
EN 60601-1-6: 2007 *(IEC 60601-1-6: 2006)* *(IEC 60601-1-6: 2004)*	Medical electrical equipment Part 1-2: General requirements for safety – Collateral standard: Usability
EN ISO 10993-1: 2009 / AC : 2010 *(ISO 10993-1: 2009)*	Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process
EN ISO 10993-5: 2009 *(ISO 10993-5: 2009)*	Biological Evaluation of Medical Devices – Part 5: Tests for in Vitro Cytotoxicity
EN ISO 10993-10: 2009 *(ISO 10993-10: 2009)*	Biological Evaluation of Medical Devices – Part 10: Tests for Irritation and Delayed-Type Hypersensitivity
EN 980: 2008	Graphical symbols for use in the labelling of medical devices
EN 1041: 2008	Information supplied by the manufacturer with medical devices

2.5 Summary of the necessary training and experience needed to use PULMOVISTA 500

During the initiation visit of each trial site a training has to be performed by a representative of Drägerwerk AG & Co. KGaA introducing the use of the device and standardized data acquisition for study purposes.

3 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL TRIAL

3.1 BACKROUND

Acute Lung Injury (ALI) is a very common complication within the population of intensive care patients[2] [3] [4]. It has been shown that mechanical ventilation with ventilator settings which do not suit the individual requirements of the diseased lung can lead to injury of the cellular structures of the lung tissue. As a result, vascular and alveolar permeability increases and interstitial edema formation occurs. Due to the increased weight of the lung, alveolar collapse may predominantly occur in the independent lung regions, resulting in even more severe hypoxemia[5] [6].

3.2 IMPACTS OF STUDY RESULTS

The results of this study will help us to define the capability and reliability of PulmoVista 500 to detect changes in both global and regional ventilation. As this is a non-invasive, observational trial, we neither do expect a positive nor a negative impact on the actual study participants. The results will, however,

---

[2] Rubenfeld GD. Epidemiology of acute lung injury. Crit Care Med 2003; 31:S276-S284.

[3] Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, Bion J, Romand JA, Villar J, Thorsteinsson A, Damas P, Armaganidis A, Lemaire F; ALIVE Study Group. Epidemiology and outcome of acute lung injury in European intensive care units. Intensive Care Med 2004; 30:4-6.

[4] Goss CH, Brower RG, Hudson LD, Rubenfeld GD; ARDS Network. Incidence of acute lung injury in the United States. Crit Care Med 2003;31:1607-11.

[5] Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, Rossi G, Fumagalli R, Marcolin M, Mascheroni D, Torresin A. Relationships between lung computed tomographic density, gas exchange, and PEEP in Acute Respiratory Failure. Anesthesiology 1988; 69: 824-832

[6] Spiro SG, Silvestri GA, Agusti A (2012). Clinical Respiratory Medicine. (4th edition) Elsevier, ISBN-13- 9781455707928.

improve our knowledge about the EIT technology and thus aid the use of this technology for the benefit of future patients.

Additionally, detailed analysis of the recorded data will be very valuable for future directions of both clinical research and clinical applications of the EIT technology.

Furthermore this study will provide data needed for authorization in other countries e.g. Japan.

4 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

4.1 ANTICIPATED CLINICAL BENEFIT AND ANTICIPATED ADVERSE DEVICE EFFECTS

Anticipated clinical benefit:

By participating in the clinical study, the patient benefits of a close monitoring as part of the study, which goes beyond the clinical routine.

Anticipated adverse device effects:

The use of the device according to the normal conditions of use, may cause skin irritation to the patient or pressure marks caused by the electrode belt.

4.2 RESIDUAL RISKS ASSOCIATED WITH THE INVESTIGATIONAL DEVICE, AS IDENTIFIED IN THE RISK ANALYSIS REPORT

Residual Risk associated with the Investigation Device:

PulmoVista 500 is a CE released class IIa medical device. According to the risk analysis for the conformity assessment according to the ISO 14971 there exists no unacceptable individual or overall residual risk for the medical device.

Risks associated with participating in the clinical trial:

Since the study is a non-interventional observational study without additional study-related changes in the treatment of patients, no additional study risks occur through the participation in this clinical study.

4.3 POSSIBLE MUTUAL REACTIONS

The use of the device according to the normal conditions of use, may cause skin irritation to the patient or pressure marks caused by the electrode belt.

(see above 4.1)

4.4 PROCEDURE TO REDUCE RISKS

As described in the instructions for use of the device the patient's skin should be checked periodically for any discomfort or injury.

In case of intolerance reactions, signs of progressive infection, skin reactions or mechanical irritation, which go beyond the usual extent, the measurement is interrupted and an adequate therapy initiated. The patient will be requested to report problems immediately to the investigator.

5 OBJECTIVES AND HYPOTHESES

5.1 OBJECTIVES

5.1.1 PRIMARY STUDY OBJECTIVES

To assess the capability of PulmoVista 500 to continuously monitor ventilation and its changes.

5.1.2 SECONDARY STUDY OBJECTIVES

- To assess the capability of PulmoVista 500 to detect regional changes of ventilation and lung volume.
- Documentation of any safety events related to the use of PulmoVista 500
- Assessing the use specific clinical helpfulness of PulmoVista 500

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 GENERAL

The clinical trial will be conducted according to the German Medical Device Act as § 23 b clinical trial. There is no need to access an approval by federal authority (BfArM).

The trial can start only after obtaining a positive review by all local Ethics Committees. The written approval of the EC and written exemption of approval must be filed in the Sponsor File. Additionally, every participating site must receive a copy of these documents to be filed in the Investigator Site File (ISF).

6.1.1 TYPE, DESIGN, PRINCIPAL INVESTIGATOR

The trial is a multicenter observational study. This study will be conducted in compliance with ISO 14155. It is sponsored by Drägerwerk AG. Drägerwerk AG assumes all responsibilities as the sponsor of this study.

Coordinating Investigator: PD Dr. med. Peter Spieth
Universitätsklinikum Carl Gustav Carus
Dresden

Medical Advisor: Associate Professor (USA)
Dr. med. Oliver C. Radke
Klinik für Anästhesiologie
und Operative Intensivmedizin
Klinikum Bremerhaven-Reinkenheide gGmbH

6.1.2 BLINDING

This is an observational trial of intraindividual correlation between two methods of measurement. Since we do not allocate patients to treatment and placebo groups as it would be the case in a randomized trial, blinding is not strictly necessary. However, patients will be blinded to the results of the investigational EIT device by either a) being sedated in the ICU or under general anesthesia or b) device will not be facing them so they cannot see the results.

Study personnel at bedside will not be blinded as they have to interact with the device (to ensure quality of data recording) and therefore blinding is not feasible.

The medical personal responsible for the patient´s medical care does not use the information given by the PulmoVista 500 .

6.1.3 PRIMARY AND SECONDARY STUDY ENDPOINTS

PRIMARY STUDY ENDPOINT
The capability of PulmoVista 500 for continuous monitoring of ventilation and its changes at different points in time during varying states of regional ventilation, the cross-correlation function (CCF) between global tidal impedance (EIT) waveforms and global tidal volume (ventilator) curves will be evaluated.

SECONDARY STUDY ENDPOINTS

- First secondary endpoint: To assess the capability of PulmoVista 500 to detect changes in regional ventilation by evaluating the cross correlation between impedance waveforms derived from PulmoVista 500 and volume curves derived from ventilator during one-lung-ventilation.
- Assess that changes of tidal volumes induced by ventilator settings can be monitored by the "Trends view"
- Assess that changes of the end-expiratory lung volumes (induced by e.g. PEEP changes, recruitment and suctioning maneuvers) can be monitored by "dEELI trend view"

- Documentation of any safety events related to the use of PulmoVista 500
- Assessing the use specific clinical helpfulness of PulmoVista 500 - clinical helpfulness of PulmoVista 500 is proven if
    - see attachments (chapter 23.1) clinical usability

6.1.4 INVESTIGATION OF ENDPOINTS

The trial relevant data has to be recorded in time in the electronic CRF. The use of the eCRF (MACRO 4) makes it possible to provide the raw data in CDISC readable standard. Electronic data of EIT, CT-, MRI-images, ultrasound assessments and radiographs, only marked with the subject identification number, will also be transferred to the KKS cloud in patient specific folders.

6.1.5 STUDY RELEVANT DEVICES

The serial numbers of all used devices will be documented in the respective ISF and the TMF.

The recording of the measurements will be pseudonymised.

- PulmoVista 500: This is a device that can measure and visualize global and regional impedance among a cross-section of a patient´s thorax. The device uses very low alternating currents administered to the patient´s chest through an electrode belt. The measurement is non-invasive, radiation free and yields results in real time (see above 2.4).
- Ventilator: A standard patient ventilator with a compatible data interface to PulmoVista 500 (e.g. Draeger V500 or Evita XL) to allow recording of ventilation data by PulmoVista 500 .
- Laptop: Standard laptop computer running software (Synology Cloud Station Drive, respective current version) to transfer data from PulmoVista 500 to the KKS cloud (imbcloud.medizin.tu-dresden.de).
- USB-Flashdrive to transfer the data determined during measurements to the statistician via laptop and KKS cloud (see above and below Datamanagement). Access to the Flashdrive reserved to specially authorised users.

6.1.6 PROCEDURES TO REPLACE PARTICIPANTS

As this study does not have treatment arms, replacement of participants is not necessary. The calculated sample size includes a safety margin for dropouts.

6.2 CONCOMITTANT MEDICAL MANOUVERS

The medical care of the patient will not be altered by this purely observational trial. We do however capture data while medical care is being altered (e.g. changes in ventilator settings), but these changes are in no way affected by the study protocol.

6.2.1 EXPOSITION TO MEDICAL DEVICE

All devices are approved acc. Medical Device Act and will be used accordingly.

Measurement with PulmoVista 500 during ventilation shall last for a maximum of eight hours.

6.2.2 USE OF MEDICAL DEVICE

All devices are used according to their intended purpose according to the user manuals and the standard training of the users ("Geräteeinweisung").

6.3 PARTICIPANTS

6.3.1 INCLUSION CRITERIA

A potential subject will be included in the study if he/she meets all of the following inclusion criteria:

- Male and female patients (18 years of age or older),
- On respiratory support in ICU care or scheduled for such (e.g. postoperatively) or scheduled for surgery with OLV
- Patients of which the monitoring of ventilation distribution may be of clinical interest,
- Patients being ventilated via an artificial airway with a mechanical ventilator that is compatible with PulmoVista 500
- Patients scheduled for changes in ventilation settings that may cause relevant changes in the ventilation
- Chest circumference between 70 and 150 cm,
- Written informed consent to participate in the study provided by either the patient or the legal representative of the patient.

6.3.2 EXCLUSION CRITERIA

A potential subject will be excluded from the study if he/she meets any of the following criteria:

- Currently has a permanent or temporary pacemaker, implantable cardiac device (ICD) or other device emitting electrical energy,
- Has a BMI ≥ 50,
- Has a tidal volume (V_T) ≤ 200 mL,
- Current uncontrolled body movements such as tics, tremors or seizures,
- Current wound dressings or infections on the chest that might interfere with the electrode belt placement,
- Women of child bearing potential whose pregnancy cannot be excluded based on a pregnancy test or other proven facts.
- Allergic to materials used in the electrode belt,
- Participation of the patient in an interventional trial within the last four weeks before enrollment in this trial

- Evidence suggesting that the patient or his legal representative is not likely to follow the trial protocol (e.g. lacking compliance),
- infectious diseases that require isolation of patient (e.g. MRSA),
- Concomitant use of an air anti-decubitus medical mattress with dynamic inflation that cannot be deactivated during EIT measurements.

6.3.3 POPULATION AND INDICATION

- Intensive care unit (ICU) patients, who are mechanically ventilated via an artificial airway (endotracheal tube or tracheostomy cannula) and who are expected to be subjected to major changes in their ventilator settings will be monitored with the PulmoVista 500 device before, during and after the changes. These changes in the ventilator settings should result in recognizable changes in the distribution of ventilation in the lungs.

  Examples of such interventions are:

  - Spontaneous breathing trial (SBT) using the ventilator (as opposed to SBT using a T-piece)
  - Switching between different modes of ventilation (e.g. volume controlled, pressure controlled, pressure support, CPAP)
  - Initial adjustment of ventilation after ICU admission
  - Weaning of ventilation in preparation of extubation
  - PEEP trials and recruitment maneuvers
  - Suctioning maneuvers
- Patients who are scheduled for surgeries that require blocking of one bronchus (e.g. one-lung-ventilation by insertion of a double lumen tube or bronchial blocker)

6.3.4 DURATION AND TIMELINES OF THE CLINICAL INVESTIGATION

Successful enrollment of the entire study cohort is expected to be completed within 12 months.

6.3.5 DURATION PER PARTICIPANT

Data acquisition per patient is anticipated to be completed within eight hours. Additional patients will be evaluated for any adverse events on day 1, 2 or 3 after the study day. No further follow up for the purposes of the clinical study is required.

6.3.6 NUMBER OF PARTICIPANTS

A sample size of n=80 patients (including at least 25 patients with OLV) has been calculated with an assumed drop-out rate of 15%.

6.3.7 RECRUITING TIMELINE

Recruiting time (FPFV – LPFV): 01/2017 – 09/2017

6.4 STUDY PROCEDURES

6.4.1 VISIT 1 - SCREENING AND INFORMED CONSENT

Patients are considered "enrolled" when written informed consent has been obtained and all in- and exclusion criteria are appropriately met.

6.4.1.1 PATIENTS WHO ARE NOT YET ADMITTED TO ICU

Patients who are not jet admitted to ICU will be screened preoperatively, e.g. during the preoperative evaluation by the anesthesiologist. The physicians responsible for the patients´ medical care will inform the study team when the actual medical intervention is planned. Study personnel will have a screening checklist to identify patients who might be eligible to participate (e.g. scheduled for thoracic surgery or patients who are scheduled for major surgery that most likely requires postoperative sedation and weaning in the ICU).
If patients confirm interest in participating in this study, investigator will evaluate inclusion and exclusion criteria according to the checklist. If all in- and exclusion criteria are appropriate, investigator will explain the study protocol to the patient and obtain written consent.

6.4.1.2 PATIENTS WHO ARE ALREADY IN THE ICU

Patients who are already in the ICU will be screened by study personnel by interviewing the physicians responsible for patient care in the ICU. Study personnel will use a checklist to determine if a patient is expected to undergo a change in ventilation situation that is appropriate for inclusion in the study (e.g. spontaneous breathing trial, changes in PEEP settings). Study personnel will then approach the patients´ legal representative (e.g. person in charge to explain the study protocol and obtain written consent.

Demographic data, patients´ medical history and lab tests are obtained from the anesthesia record and the ICU chart as appropriate. The study protocol does not require any additional tests besides medically indicated by the physicians in charge of the patients.

6.4.2 VISIT 2 - MEDICAL AND STUDY MEASUREMENT

6.4.2.1 PATIENTS CURRENTLY ON OR SCHEDULED FOR VENTILATOR CARE IN THE ICU

The physicians responsible for the patients´ medical care will inform the study team when the actual medical intervention is planned. Study team will re-evaluate whether all in- and exclusion criteria are appropriately met (e.g. still intubated).

Study team will setup the investigational devices at least 30 minutes before the medical intervention to allow for stable baseline readings and uninterrupted medical care. PulmoVista 500 electrode belt is placed around the patient´s chest, and the PulmoVista 500 is connected to the ventilator. Continuous recording of data is started and verified.

During the investigational phase, the study device will continuously record all data. Before the study measurement, the study team will record baseline readings for at least 5 minutes. During the study measurement, recording will continue uninterrupted; exact time points of events (e.g. when vent settings are adjusted) and details of the study measurement (e.g. old and new vent settings) are recorded by the study personnel according to the clock in PulmoVista 500 (to ensure accurate timing with the recorded data). Recording of the data will continue for at least 5 minutes after the medical intervention is completed.

Once the recording is completed, electrode belt will be removed from the patient and the investigational device will be disconnected.

6.4.2.2 PATIENTS SCHEDULED FOR ELECTIVE SURGERY WITH OLV

Patients scheduled for elective surgery will receive medical care according to the hospital´s established standards. Before anesthesia induction, study team will re-evaluate whether all in- and exclusion criteria are appropriately met (e.g. still intubated). Patients are considered "enrolled" when written informed consent has been obtained and all in- and exclusion criteria are appropriately met.

After arrival in the induction room, patients will be connected to the appropriate monitors for routine patient care. Additionally, patients will be asked to sit up and have the electrode belt of PulmoVista 500 fitted to their thorax according to the IfU. Investigational device is set up and connected to the patient and related devices.

Before and during pre-oxygenation of the patient, study personnel will start and test recording of the data. Anesthesia induction, placement and confirmation of correct placement of the DLT / bronchial blocker will be performed according to the hospital´s established standards of care.

In patients who require independent lung ventilation during their surgical procedure, EIT measurements shall be performed during normal (both lungs) and single-lung ventilation after induction of anesthesia before start of surgery. According to standard of care correct positioning of the DLT respectively of the bronchial blocker will be tested by switching between normal ventilation and single-lung ventilation (right and left lung will be tested independently).

During the anesthesia induction, study personnel will note the time of particular events (e.g. start of induction, mask ventilation, intubation, clamping left/right) by using the clock on PulmoVista 500. The physician in charge of the anesthesia will be asked to allow uninterrupted baseline readings of at least 2 minutes after successful intubation and to keep the left and right lumen of the DLT clamped for at least 1 minutes each to ensure stable recording of the data. Each step of the testing of correct placement of the DLT or the bronchial blocker will be marked in PulmoVista 500 before the conduct of this step.

Once data have been completely recorded and anesthesia induction is completed, the physician in charge will record approx. 2 minutes and stop the recording afterwards. The electrode belt will then be disconnected from the patient. This concludes the study for this particular patient. Typically, the patient is now transported to the operating room for their surgical procedure; this is not part of the study protocol.

6.4.3 GENERAL

In both cases, if the physicians responsible for the medical care of the patient decide that the data recording for the study purpose interferes with necessary medical care (e.g. in case of cardiac arrest), the data recording will immediately be stopped, the electrode belt removed and every effort will be undertaken to not interfere with the medical care. In this case, the patient will be considered a drop-out.

All obtained data were recorded immediately in the eCRF provided by the KKS Dresden or were transferred to the KKS cloud.

Electronic data of EIT, CT-, MRI-images, ultrasound assessments and radiographs, only marked with the subject identification number, will also be transferred to the KKS cloud. These data were not taken especially for this study, but due to necessary medical treatment. They will be used within this study if they were taken during the period of day −2 to +3.

6.4.4 VISIT 3 - FOLLOW-UP-VISIT

All patients who underwent data recording will be followed up once within 1-3 days after visit 2. During this follow up visit, patients will be asked about any adverse events, and the patients´ thorax will be visually inspected for any irritation caused by the electrode belt. If patients are not able to answer (e.g. still sedated or unconscious), the physicians taking care of the patient are questioned about any adverse events.

6.5 RESPONSABILITYS OF SPONSOR AND INVESTIGATOR

The **Sponsor** (Drägerwerk AG) has the overall responsibility for the clinical trial including initiation, organization, and financing (according to the German Medical Device Act).

The sponsor and the clinical investigator assure that the clinical trial is performed in accordance with:

- DIN-EN-ISO 14155: 2011,
- Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, Washington 2002, Tokyo 2004, Seoul 2008, Fortaleza 2013).

This trial must be carried out in compliance with the protocol.

All investigators are licensed to practice medicine and have at least two years work experience in intensive care and anesthesia. All investigators have theoretical and practical experience in treating mechanically ventilated patients.

All investigators have theoretical and practical experience in conducting clinical trials and provide documented proof of GCP knowledge and/or investigator's training as well as knowledge of German Medical Devices Act.

The Coordinating investigator must have at least two years of experience in conducting clinical trials.

The investigator at each trial site is responsible for selecting and assembling the study team members (especially the medical staff) according to the requirements of this trial protocol. Furthermore, the investigator is responsible for training and supervision of the study team and providing all necessary information. This has to be documented.

6.6 MONITORING

The investigator agrees that the monitor will visit the trial site in appropriate intervals. During these visits the monitor will check the quality of the data recording and ensure that the trial site adheres to the timeframe as set in the study protocol. The investigators agree to provide any relevant information and documentation whenever the monitor requires that. This includes access to all original study documents and source data.

It is the responsibility of the investigator to keep the participant's chart as complete as possible (e.g. history, concomitant diseases, inclusion in the clinical study, visit dates, results of laboratory tests, distribution of the study medication, and adverse events). Source data are checked and compared with entries in the data bank. The participant has given consent with this procedure by signing the patient information and written informed consent form.

Tasks of the monitor and the quality assurance will be described in detail in a monitoring manual.

The monitor has the responsibility to treat all information confidentially and to safeguard the integrity and personal privacy of the study participants.

7 STATISTICAL CONSIDERSATIONS

7.1 SAMPLE SIZE, DROP-OUT-RATES, LEVEL OF SIGNIFICANCE AND POWER OF THE CLINICAL INVESTIGATION

Primary Endpoint (Efficacy)

Based on former porcine trials[7] with PulmoVista 500 and data from clinical studies with other EIT devices the sample size was calculated using the program G*Power 3.1.9.2.

An α-error of p = 0.05 and a power = 0.9 in a two-sided testing resulted in a sample size of 68 patients. With this sample size a difference of 0.1 of the mean cross-correlation coefficient shall be detected, i.e. the true value of a calculated mean of 0.8 will not be smaller than 0.7 and not be larger than 0.9 with the given p-value and power under the assumption of a standard deviation of less than .25.

Accounting for 15 % potential drop-outs 80 patients shall be enrolled in the study.

Secondary Endpoint (Efficacy)

Based on former porcine trials with PulmoVista 500 and data from clinical studies with other EIT devices the sample size was calculated using the program G*Power 3.1.9.2. An α-error of p = 0.05 and a power = 0.9 in a two-sided testing resulted in a sample size of 22 patients. With this sample size a difference of 0.1 of the proportion between reference and investigated variable shall be detected.

Accounting for 15 % potential drop-outs 25 patients shall be enrolled in this subgroup of the study.

7.2 STATISTICAL DESIGN

Null-Hypothesis

The PulmoVista 500 is not capable of continuously monitoring ventilation.

Primary Endpoint (Efficacy)

To assess the capability of PulmoVista 500 for continuous monitoring of ventilation and its changes at different points in time during varying states of regional ventilation, the cross-correlation function (CCF) between global tidal impedance (EIT) waveforms and global tidal volume (ventilator) curves will be evaluated.

- To refute the null-hypothesis of this trial it must be shown that the global tidal impedance waveforms and the global tidal volume curves correlate

[7] Fischer E, Gremse F. Assessment of the capability of PulmoVista® 500 to continuously monitor regional ventilation distribution and its changes over time. An Animal Study. FINAL STUDY REPORT. PulmoVista 500-30022. Aix Scientifics. 2016-01-27

significantly, i.e. that the correlation scores are significantly different from zero.

- If the null-hypothesis is refuted the capability of PulmoVista 500 is assumed to be a valuable diagnostic device for long-term monitoring of mechanical ventilation.

The mean value of the intra-subject cross-correlation function (CCF) between global impedance (EIT) waveforms and global volume (ventilator) curves will be determined.

Secondary Endpoint (Efficacy)

To assess the capability of PulmoVista 500 to detect regional changes of ventilation it shall be tested, whether EIT can correctly differentiate between normal and single-lung ventilation.

- To refute the null-hypothesis of this trial it must be shown that the regional information about tidal impedance variation matches the clinical changes from normal to single-lung ventilation, i.e. that EIT detects ventilation vs. no ventilation in each lung.
- If the null-hypothesis is refuted the capability of PulmoVista 500 is assumed to be a valuable diagnostic device for detecting regional ventilation changes during long-term monitoring of mechanical ventilation.

The diagnostic output of the EIT measurements will be compared with clinical ventilation settings in a 2x2 table.

7.3 PASS/FAIL CRITERIA

There is no pass/fail criteria defined.

7.4 INTERIM ANAYLSIS

There is no interim analysis planned.

7.5 CRITERIA FOR THE TERMINATION OF THE CLINICAL INVESTIGATION ON STATISTICAL GROUNDS

There are no termination criteria defined.

7.6 PROCEDURES FOR REPORTING ANY DEVIATIONS FROM ORIGINAL STATISTICAL PLAN

Any deviations on the original statistical plan will be documented and any changes leads to a new version of the statistical plan.

7.7 SPECIFICATION OF SUBGROUPS

Twenty-five patients with OLV during anesthesia for thoracic surgery (secondary endpoint efficacy).

7.8 PROCEDURES THAT TAKE INTO ACCOUNT ALL DATA

The Full Analysis Set (FAS) consists of all enrolled patients. This excludes non-informative drop-outs. A per protocol analysis may be specified in the statistical analysis plan excluding major protocol violations.

Safety Analysis Population (SAP) consists of all enrolled patients who already were treated with the medical device (PulmoVista 500).

7.9 TREATMENT OF MISSING, UNUSED OR SPURIOUS DATA, INCLUDING DROP OUTS AND WITHDRAWALS

No missing data imputation techniques will be applied, and patients with missing efficacy data will used as censored in the time to event analysis. Therefore any effort should be undertaken to avoid missing data, notably in case of the primary outcome measures.

When a patient is withdrawn from the trial before the scheduled end of a measurement phase, and an end-of-study visit can be performed, the data of this visit will be used for computing the primary outcome measure.

The handling of missing data will be specified in the SAP prior to the final statistical analysis based on assumptions on the respective missingness mechanisms or in the Data Review Meeting.

8 DATA UND DATAMANAGMENT

The electronic Case report Form (eCRF) for capture of the pseudonymised study specific data according to the protocol, will be designed by the KKS Dresden in cooperation with the Medical Advisor. The eCRF will be programed and validated at a clinical study database with the EDC study specific software MACRO 4.0 (Elsevier) according ICH-GCP and to the Standard Operating Procedures (SOPs) of the KKS Dresden.

During the whole course of the study, a backup of all data is made on a daily basis. Unauthorized access to patient and site data is prevented by the access concept of the study database which is based on a strict hierarchy and role model and managed by KKS Dresden.

The investigator has to authorize member(s) of the study team at the study site(s) for data capture and sign of eCRF data. This authorization has to be supplied via Staff Signature and Delegation Log to the KKS for setup the user at the database. The study specific data will be entered directly into the

database via eCRF data entry masks by authorized member of the study team.

The eCRF will be filled in shortly after each study visit. Each eCRF Visit will be signed electronically by an investigator or a therefore authorised member of the study team by their login identification. This represents the electronic equivalent of a signature on paper and confirms accuracy and authenticity of all data on the eCRF.

An eCRF will be provided for each patient. The patient will be identified as per the Patient-ID only. All information required by the protocol and therefore collected during the clinical trial must be recorded by an investigator or an authorised member of the study team as source data in the source documentation for the study.

Source data according to DIN EN ISO 14155:2012-01 are defined as all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. Source data are contained in source documents (original records or certified copies). It is defined for each trial site, what source data for respective eCRF entries are and where these are filed (Source Data Agreement).

Data recorded in the PV500 are only marked with the subject identification number (see below 8.2). At the end of every visit 2, when the patient is no longer connected to the PulmoVista 500, the new data will be transferred to the study laptop and were synchronized with the site folder in the KKS cloud. The synchronization will be performed via an encrypted connection. For data transfer between PulmoVista 500 and study laptop a standard USB-Flashdrive will be used.

Electronic data of CT-, MRI-images, ultrasound assessments and radiographs, only marked with the subject identification number, will also be transferred as described above.

At the end of the trial a final check of all collected data (via KKS Cloud) will be performed.

However, the **Investigator has final responsibility** at all times for the accuracy and authenticity of all clinical and laboratory data entered in the eCRF.

At the end of the study the Investigator will receive the trial specific data including the audit trail concerning his/her investigational site on electronic data storage.

8.1 PROCEDURES USED FOR DATA REVIEW, DATABASE CLEANING, AND ISSUING AND RESOLVING DATA QUERIES

The review of these data will be performed by the programmed ranges-, validity- and consistency checks at the data capture. Errors, missing or

generated discrepancies, by the database, monitoring or data management have to be answered by the authorized member of the study team.

All changes of each data will be tracked with the old and changed value by username, reason for change, date- and timestamp (audit trail) of authorized member of study team.

At the end of the study, once the database has been declared complete and accurate, the database will be locked. Thereafter, any changes to the database are possible only by joint written agreement between coordinating investigator, biometrician and data manager.

8.2 SUBJECT IDENTIFICATION NUMBER

Patients fulfilling the inclusion and exclusion criteria will get an identification number at registration. Subject ID number consists on a combination of site ID number (XX) and a sequential number for each subject (YYY, starting with "001" at each site).
An example: Subject ID: 02-003

8.3 VALIDATION AND SECURING ELECTRONIC DATABASE SYSTEMS

MACRO 4.0 is running in a validated state in a controlled environment and corresponds to all requirements from FDA 21 CFR Part 11 and EU GMP Annex 11. MACRO is running behind a firewall with separated application and database servers.

8.4 ARCHIVING OF DATA AND DURATION

All essential clinical investigation documentation (Trial Master File), the electronically stored data, the study specific eCRF data inclusive the audit trail on an electronic data media and the final report will be stored for at least 10 years at the Sponsor after the investigation's completion.

At the trial sites, the investigators' files, patient identification lists, signed written consent forms, the study specific eCRF data inclusive the audit trail on an electronic data media and the patients' files will be stored for at least 10 years after the investigation's completion. If local rules or other legal requirements require longer periods of archiving, then these have to be met.

9 AMENDMENTS

No changes in the study procedures shall be effected without mutual agreement of the coordinating investigator and the sponsor. All changes must be documented by signed clinical protocol amendments. Substantial changes may require approval from the EC (as applicable) prior to implementation. Under emergency circumstances, deviations from the trial protocol to protect the rights, safety and well-being of human subjects may proceed without

prior approval of the sponsor. Such deviations shall be documented and reported to the sponsor.

Changes made to the protocol that were appraised positively by the Ethics Committee must be positively reappraised and approved if the changes

- are such that they may affect the subjects' safety, e.g. fundamental changes to the therapeutic or diagnostic procedures,
- result in further data collection that necessitates changes to the patient information and/or Informed Consent Form,
- affect the interpretation of the scientific documents upon which the trial is based or the significance of the results of the trial,
- significantly affect the leadership or conduct of the trial,
- concern the quality or the innocuousness of the medical device.

10 ADHERENCE TO THE PROTOCOL

After a patient has been enrolled, it is the investigator's responsibility to avoid protocol violation in order to obtain unbiased data for the trial.

All protocol violations must be documented by the investigator. Those protocol violations that are to be deemed major will be reported to the coordinating investigator and to the sponsor immediately.

Minor variations are inevitability, but must be documented together with a justification.

All protocol violations will be discussed with the responsible biometrician before closing the data bank and carrying out the statistical analysis.

The reason for a violation shall be clarified to avoid this in future.

The investigator must ensure that the recorded data are documented as per protocol.

11 DEVICE ACCOUNTABILITY

The Serial number of every provided Medical Devices and accessory component per patient (electrical cables, electrode belt, trunk cable) for each trial site will be documented in the delivery notifications and stored in TMF and ISF.

12 STATEMENTS OF COMPLIANCE, INSURANCE

12.1 STATEMENT OF COMPLIANCE

The sponsor and the clinical investigator assure that the clinical trial is performed in accordance with:

- Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, Washington 2002, Tokyo 2004, Seoul 2008, Fortaleza 2013),
- National and local regulations.

This trial must be carried out in compliance with the protocol and in accordance with the sponsor's standard operating procedures. The **investigator** agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of DIN EN ISO 14155:2012-01.

The responsibilities of the investigator include:

- understanding of the properties of the trial medical device as described in the trial description
- execution of the measurement plan,
- providing sufficient time and capacity to perform the clinical trial,
- correct collection and documentation of trial related data and reporting,
- provision of data to the sponsor, for the monitor, and for audits/inspections,
- ensuring strict confidentiality and requesting similar confidentiality from her/his staff concerning information about participants and information provided by the sponsor. Trial documents provided by the sponsor (protocols, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial,
- The clinical investigator has full responsibility for the conduct of the clinical trial in the trial center.

12.2 INSURANCE

As this study is a non-risk study (*medical device is CE certified and it is used according to its approved intended use. The study does not expose the patient to any harmful or stressful interventions*) which is to be approved according to the §23b of the German Medical Device Act (MPG), insurance is covered by the sponsor's general product lability insurance.

This insurance is provided by the following insurer:
HDI Global SE
Hamburg Branch
Überseering 10a
22297 Hamburg
Germany

Policy Number: 20000536 01055 114

The sponsor insurance department is to be contacted at:
Drägerwerk AG & Co. KGaA
Corporate Insurance
Mr. Andy Martens
Moislinger Allee 53-55
23558 Lübeck
Germany
phone: +49 451 882 5060

13 INFORMED CONSENT PROCESS

The patient's informed consent must refer explicitly to the collection and processing of health-related data. Therefore the patient should be informed explicitly about the purpose of collecting the data and scope of what is to be collected and that personal data, in particular those related to health, will be used.

The investigator must obtain written informed consent from the patient for his/her inclusion in the study, after explaining the rationale for and the details, aims and objectives of the study, the risks and benefits of alternative measurements, and the extent of the patient's involvement. The patient shall have time to read and understand the Informed Consent, and shall personally date and sign the Informed Consent. The patient should also be provided a copy of the signed Informed Consent.

The investigator is responsible for ensuring that no patient is subject to any study-related examination or activity before the patient has given his/her written informed consent.

After obtaining signature of the patient, duly signed informed consents, as well as written information given to patients, shall be kept and archived in the

Investigator file for a minimum of 10 years after completion of the investigation.

All information provided to patients including any advertisements for the clinical investigation within the clinical trial sites or in the public press needs approval of both sponsor and EC prior to being presented to the patients under any format.

If new information becomes available that can significantly affect a subject's future health and medical care that information shall be provided to the subject(s) in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

Informed consent process with subjects who are not able to give written informed consent will be carried out by the subject´s legal representative. (6.4.1.2)

14 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

14.1 DEFINITION ADVERSE EVENT (AE)

Adverse events are defined in accordance with ISO 14155:2011. That is, an Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including clinically significant abnormal laboratory findings) in subjects, users or other persons, whether or not the adverse event is related to the used medical device. This definition includes events related to the medical device or events related to the procedures involved in the study.

Medical conditions present at baseline will not be recorded as adverse events during the study unless they deteriorate, becoming more severe or more frequent.

14.2 DOCUMENTATION AND REPORTING OF AE(S)

Information on AEs will be collected from the time of enrollment until regular completion of study, death or withdrawal (whichever comes first). The investigator will report all AEs as soon as possible (preferably within 7 days of the site's knowledge of the event) by entering them in to the eCRF.

AEs are documented on an AE form (eCRF). Diagnosis, onset, and end of the AE, seriousness, severity, causal relationship with the investigational medical device, with the study procedures, treatment of the AE, and the outcome of the event will be documented. The Investigator will follow-up the event until the AE has been resolved, resolved with sequelae or was fatal.

15 SERIOUS ADVERSE EVENTS (SAE)

Information on Serious Adverse Events will be collected from the time of visit 2 until visit 3.

A Serious Adverse Event (SAE) is in accordance with ISO 14155 an AE that led to death, led to serious deterioration in the health of a subject that resulted in either a life threatening illness or injury, or permanent impairment of a body structure or a body function, in-patient or prolonged hospitalisation or medical or surgical intervention to prevent life-threatening illness or permanent impairment to a body structure or body function or led to foetal distress, foetal death or a congenital abnormality or birth defect.

Planned hospitalisations for pre-existing conditions or a procedure required by the protocol, without serious deterioration in health, is not considered a serious event. If hospitalisation or extension of hospitalisation results as a consequence of a complication in a pre-existing condition or a procedure required by the protocol then it will be recorded as an SAE.

Note: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

15.1 DOCUMENTATION AND NOTIFICATION OF SAE – INVESTIGATORS RESPONSIBILITY

Serious Adverse Events will be documented on the eCRF.

They must be documented in the eCRF immediately and not later than 24 hours after the investigator's knowledge of the event. Follow-up information should also be reported immediately after awareness.

The Sponsor will have read authorization for the eCRF. In this way the Sponsor will get timely information by the system.

16 DEVICE DEFICIENCY (DD)

16.1 DEFINITION DEVICE DEFICIENCY (DD)

Device deficiencies (DDs) are defined in accordance with ISO 14155 as any inadequacy of a medical device with respect to its identity, quality, durability, reliability safety or performance, including malfunctions, use errors, and inadequate labelling.

A malfunction is defined as failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol.

All device deficiencies shall be documented during the clinical investigation and reported to the sponsor as soon as possible (preferably within 7 days of the site's knowledge of the event) by entering them in to the eCRF.

Drägerwerk AG & Co. KGaA will be informed about device deficiencies as described in the Vigilance-Plan of the Study.

16.2 DEFINITION AND REPORTING OF INCIDENT

An incident is a malfunction, failure or a modification of the features or performance or an inaccurate label or instruction manual for a medical device, which directly or indirectly caused, may have caused in the past, or may cause in the future, death or a serious aggravation of the state of health of a patient, a user or another person (MPSV § 2 (1)).

As per MPSV §3 (2) those responsible for the first placing on the market of medical devices are obligated to report incidents that occur in Germany as well as product recalls taking place in Germany to the Federal Institute for Drugs and Medical Devices (BfArM). Reporting must be performed analogously for incidents that occur in all other participating European Countries to the responsible Authorities.

As per MPSV §3 (2) the Investigator also has to report any incident immediately to his Competent Authority and in parallel to the manufacturer using the forms provided by the BfArM for Germany and the equivalents for all other participating countries.

Incidents related to the PulmoVista 500 system or other medical devices provided by Dräger have to be reported by the investigator to:

Drägerwerk AG & Co. KGaA
Moislinger Allee 53-55
23558 Lübeck, Germany
Fax: +49 451 882-3018
E-Mail: complaint.medical@draeger.com

Incidents related to all other medical devices used within the trial have to be reported by the investigator to the respective manufacturer as per clinical routine procedures.

The Investigator is informed about the Timelines according to the German MPSV §5 (1-2).

16.3 DEVICE COMPLAINTS

Device complaints (DCs) are any device deficiencies with regard to the study device, instructions for use, operator's manual and other product related documentation. Device complaints may or may not involve a clinical event. Any complaints on the device, instructions for use, operator's manual and other product related documentation regarding the PulmoVista 500 system shall be reported by the investigator to Drägerwerk AG using the appropriate

reporting forms. Whenever possible in case of malfunction of the study device or part of the study device, the product in question shall be returned to Drägerwerk AG for investigation. The appropriate procedure for such return shall be installed by Drägerwerk AG prior to starting the clinical investigation.

In case the device complaint resulted in serious or non-serious harm of the patient, an AE/SAE/Incident has to be reported as described in previous sections.

16.4 LIST OF FORESEEABLE ADVERSE EVENTS AND ANTICIPATED ADVERSE DEVICE EFFECTS

It is conceivable that the reusable electrode belt of the PulmoVista 500 carries pathogens from one patient to another, causing infections in a study patient. In order to minimize this risk, we a) exclude any patients with multiresistant pathogens that require isolation of the patient (e.g. MRSA) and b) establish a standardized protocol for proper disinfection of the electrode belt after each use according to the IfU.

The electrode belt consists of a silicone belt with embedded carbonized silicone electrodes. The electrodes shall coated with a conductive gel before each use to improve coupling with the patient´s skin (similar to the procedure during EEG recordings). The belt and the gel could potentially cause mechanical and chemical irritation of the patient´s skin. During pre- and post-marketing surveillance of the product, Dräger has never encountered such an event, so we consider this risk to be negligible.

As the study device is CE certified, the sponsor has conducted intensive risk analysis procedures.

The official risk management report concluded that no unacceptable individual or overall residual risk while using the device is existing.

16.5 EMERGENCY CONTACT POINTS

Safety Management	Drägerwerk AG & Co. KGaA Complaint Handling Moislinger Allee 53-55 23558 Lübeck, Germany Phone: +49 451 882-5171 Fax: +49 451 882-3018 E-Mail: complaint.medical@draeger.com
Sponsor	Drägerwerk AG & Co. KGaA Clinical Affairs Moislinger Allee 53-55 23558 Lübeck, Germany Phone: +49 451 882-2888

	Fax: +49 451 882-72888
Ethikkommissionen	Ethikkommission an der TU Dresden Fetscherstr. 74 01307 Dresden Tel.: (0351) 458 2992 Fax: (0351) 458 4369 ethikkommission@mailbox.tu-dresden.de Ethik-Kommission der MHH - OE 9515 - Carl-Neuberg-Str. 1, 30625 Hannover Telefon 0511 / 532-3443 Fax: 0511 / 532-16 3443 Ethikkommission@mh-hannover.de

16.6 EMERGENCY PROCEDURES

Because no emergency is expected, no specials procedures are determined. If, contrary to all expectations an emergency should happen, the patient will receive all necessary medical treatment.

16.7 FOLLOW UP OF PARTICIPANTS

After termination of the trial participation (visit3 or withdrawal of the informed consent) patient will get appropriate medical treatment.

17 VULNERABLE POPULATION UNDER PRESSURE

This clinical trial will not include particularly vulnerable individuals.

18 PREMATURE TERMINATION OR SUSPENSION OF CLINICAL INVESTIGATION

18.1 CRITERIA FOR PREMATURE TERMINATION OR SUSPENSION OF CLINICAL INVESTIGATION

18.1.1 INDIVIDUAL

The only circumstances in which a premature study termination (i.e. no further study visits) takes place in a patient are:

- withdrawal of informed consent,
- complete loss of contact to the patient,
- impossibility to use the medical device (PulmoVista 500) or
- death of the patient.

Note that impossibility to use the device, device failure, i.e. complete loss of function beyond repair implying final termination of device use in the patient, **does not lead to individual study termination**.

Each premature termination of the trial has to be documented by the responsible investigator. If possible date, circumstances of, reason for the termination, and - if applicable - the final status of patient should be documented in detail in source documents and eCRF.

18.1.2 OVERALL

The **sponsor** has the right to discontinue the trial due to relevant medical or administrative reasons.

Possible reasons for discontinuation by the sponsor are:

- failure in recruiting participants,
- insufficient data quality,
- unforeseen circumstances at the trial site that make the continuation of the trial impossible,
- occurrence of unjustifiable risks or toxicity,
- new scientific knowledge that does not justify continuation of the clinical trial.

Trial discontinuation will be decided by the sponsor in cooperation with the investigator.

18.2 PROCEDURES FOR PREMATURE TERMINATION OR SUSPENSION OF A SINGLE SITE

The sponsor has also the right to discontinue the participation of a site for one of the following reasons:

- failure in recruiting participants
- insufficient data quality
- no adherence to the protocol.

18.3 PROCEDURES FOR PREMATURE TERMINATION OR SUSPENSION

The responsible ethics committee will be informed of the situation and the reason for the decision. The sponsor will pick up the study equipment and the investigator has to complete the documentation.

A final report will be created on the basis of the contained data.

19 PLANNED TERMINATION OF CLINICAL INVESTIGATION

The clinical investigation report should be provided to the EC`s within 12 months after study termination. Planned Study termination will defined as last patient last visit (LPLV).

20 DATA SECURITY AND PUBLICATION POLICY

20.1 PATIENT IDENTIFICATION AND CONFIDENTIALITY

Within this study, personal data from the investigation subjects (name, initials, date of birth) and data regarding the therapy and the course of disease (medical results, types of therapy) will be collected in the trial site. The identity of subjects enrolled in the study and the information contained in their study records will be kept confidential. The data will be stored and processed in pseudonymized form (i.e. without reference to the patient's name) with the aid of an identification number.

Since in the course of the investigation contact between the trial site and the patients is necessary, the patients' full name, address and telephone number will be ascertained and stored after obtaining written permission to do so. This information will be stored separately from the investigation data.

Data will be analysed at the KKS Dresden. The safety concept ensures amongst other things that data access is limited to authorized persons, that measures are taken to prevent loss of data and that the laws pertaining to data protection are observed. The data are protected from third party access and only members of the investigation are permitted access. These members are sworn to secrecy.

In the event of withdrawal of consent, the investigation subject´s stored data must be deleted if this is requested by the subject.

20.2 DECLARATION REGARDING DATA PROTECTION

During data entry, processing and analysis in the KKS Dresden, Fetscherstr. 74, 01307 Dresden, all requirements of the data protection act will be taken into account. Access to the data is strictly limited to authorized persons. Data are protected against unauthorized access.

20.3 DECLARATION REGARDING THE PSEUDONYMIZED TRANSFER OF PERSONAL DATA

The sponsor certifies herewith that the transfer of pseudonymized personal data will take place according to the documentation and communication regulations in MPKPV-guideline §10 (5). Moreover, the sponsor certifies that persons who do not permit the transfer of data will not be admitted to the investigation.

20.4 PUBLICATION POLICY

The PV500 shall be published under the lead of the sponsor together with contributing partners Details are governed by a contract.

Additional projects not predefined in this protocol might arise during the study. Results of those projects might be published only after publication of the predefined projects, unless the responsible authors are unable to complete the respective paper within one year after the end of the study. All not predefined projects will require approval by the sponsor.

All additional publications must refer to the PV500-Trial

Prior to study start, the clinical trial will be registered in a public trial registry (ClinicalTrials.gov).

21 Signatures

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Sponsor & Projectmanager (Sponsor)

Felix Fischer 21. Nov. 2016, F. Fischer

Date, Signature

Coordinating Investigator

PD. Dr. med. Peter Spieth _____

Date, Signature

Medical Advisor (Sponsor)

Assoc. Prof. (USA) Oliver Radke _____

Date, Signature

Biometricians

Prof. Dr. med. I. Imhoff _____

Date, Signature

Uta Schwanebeck _____

Date, Signature

Projectmanager & Monitor (KKS)

Mario Graf _____

Date, Signature

21 Signatures

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Sponsor & Projectmanager (Sponsor)

Felix Fischer _____
Date, Signature

Coordinating Investigator

PD. Dr. med. Peter Spieth 22/11/16 _____
Date, Signature

Medical Advisor (Sponsor)

Assoc. Prof. (USA) Oliver Radke _____
Date, Signature

Biometricians

Prof. Dr. med. M. Imhoff _____
Date, Signature

Uta Schwanebeck _____
Date, Signature

Projectmanager & Monitor (KKS)

Mario Graf _____
Date, Signature

21 Signatures

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Sponsor & Projectmanager (Sponsor)

Felix Fischer _____
Date, Signature

Coordinating Investigator

PD. Dr. med. Peter Spieth _____
Date, Signature

Medical Advisor (Sponsor)

Assoc. Prof. (USA) Oliver Radke 11/22/2016
Date, Signature

Biometricians

Prof. Dr. med. M. Imhoff _____
Date, Signature

Uta Schwanebeck _____
Date, Signature

Projectmanager & Monitor (KKS)

Mario Graf _____
Date, Signature

21 Signatures

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Sponsor & Projectmanager (Sponsor)

Felix Fischer _____
Date, Signature

Coordinating Investigator

PD. Dr. med. Peter Spieth _____
Date, Signature

Medical Advisor (Sponsor)

Assoc. Prof. (USA) Oliver Radke _____
Date, Signature

Biometricians

Prof. Dr. med. M. Imhoff Nov 21, 2016 
Date, Signature

Uta Schwanebeck _____
Date, Signature

Projectmanager & Monitor (KKS)

Mario Graf _____
Date, Signature

21 Signatures

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Sponsor & Projectmanager (Sponsor)

Felix Fischer _____
Date, Signature

Coordinating Investigator

PD. Dr. med. Peter Spieth _____
Date, Signature

Medical Advisor (Sponsor)

Assoc. Prof. (USA) Oliver Radke _____
Date, Signature

Biometricians

Prof. Dr. med. M. Imhoff _____
Date, Signature

Uta Schwanebeck 22.11.16 _____
Date, Signature

Projectmanager & Monitor (KKS)

Mario Graf 22.11.2016 _____
Date, Signature

22 Bibliography

1. Teschner E, Imhoff M, Leonhardt S. Electrical Impedance Tomography: The realisation of regional ventilation monitoring. Drägerwerk AG & Co. KGaA 2015; Reference-Nbr 90 66 788; 19.
2. Rubenfeld GD. Epidemiology of acute lung injury. Crit Care Med 2003; 31:S276-S284.
3. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, Bion J, Romand JA, Villar J, Thorsteinsson A, Damas P, Armaganidis A, Lemaire F; ALIVE Study Group. Epidemiology and outcome of acute lung injury in European intensive care units. Intensive Care Med 2004; 30:4-6.
4. Goss CH, Brower RG, Hudson LD, Rubenfeld GD; ARDS Network. Incidence of acute lung injury in the United States. Crit Care Med 2003;31:1607-11.
5. Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, Rossi G, Fumagalli R, Marcolin M, Mascheroni D, Torresin A. Relationships between lung computed tomographic density, gas exchange, and PEEP in Acute Respiratory Failure. Anesthesiology 1988; 69: 824-832.
6. Spiro SG, Silvestri GA, Agusti A (2012). Clinical Respiratory Medicine. (4th edition) Elsevier, ISBN-13- 9781455707928.
7. Fischer E, Gremse F. Assessment of the capability of PulmoVista® 500 to continuously monitor regional ventilation distribution and its changes over time. An Animal Study. FINAL STUDY REPORT. PulmoVista 500-30022. Aix Scientifics. 2016-01-27.

23 Attachments

23.1 Clinical Usability Questionaire

Note:
This test specification is intended to validate the clinical usability of the information on ventilation distribution and lung volume changes which is displayed by PulmoVista 500.

Please respond the following questions in eCRF if this not interfere your clinical routine.

1. Select the View ***"Main".***
   How easy is it to identify within the ***Tidal Image***, whether the right and the left lung are evenly ventilated?

2. Select the View **"Main".**
   How easy is it to quantify the regional ventilation distribution as expressed by the regional parameters ***TV ROI 1 - TV ROI 4***?

3. Select the view "***End-Insp. trend***",
   Put cursor ***C1*** before and cursor ***C2*** after the intervention; View the differential image and the parameters in the trend table.
   How easy is it to set the cursors to respective positions which allow you to compare ventilation distribution before and after the intervention?

4. Select the view "***End-Insp. trend*** ",
   Put cursor ***C1*** before and cursor ***C2*** after the intervention; View the differential image and the parameters in the trend table.
   How easy is it to detect increases and/or decreases of regional ventilation?

5. Select the view "***End-Insp. trend*** ",
   Observe the global impedance waveform, and the graphical Medibus trend below the waveform and the trend table.
   How easy is it to relate the regional ventilation distribution and the corresponding parameters from the ventilator to each other?

6. Select the view "***End-Insp. trend*** ",
   Put cursor ***C1*** before and cursor ***C2*** after the intervention; View the differential image and the parameters in the trend table.
   How useful is the clinical information on ventilation redistribution caused by this intervention?

7. Select the view "***ΔEELI trend***",
   Put cursor ***C1*** before and cursor ***C2*** after the intervention; View the differential image and the dEELI parameters.
   How easy is it to set the cursors to respective positions which allows you assessing lung volume changes induced by the intervention?
8. Select the view "***ΔEELI trend***",
   Put cursor ***C1*** before and cursor ***C2*** after the intervention; View the impedance waveforms, the differential image and the dEELI parameters.
   How easy is it to detect increases and/or decreases of regional lung volume?
9. Select the view "***ΔEELI trend***",
   Put cursor ***C1*** before and cursor ***C2*** after the intervention; View the differential image and the dEELI parameters.
   How useful is the clinical information on regional lung volume changes caused by this intervention?

23.2 Clinical Plausability Questionaire

Questions addressing the regional aspects of the secondary endpoints

One of the major purposes of the pivotal clinical study

Assessment of the capability of PulmoVista 500 to continuously monitor changes of ventilation over time is to assess the plausibility of the regional information, which cannot be validated by CT scans.

The following questions are intended to validate, whether

- the regional information provided by PulmoVista 500 is plausible in the presence of certain lung conditions, which are visible in CXR or lung CT and known to cause poor ventilation
- PulmoVista 500 is capable of displaying changes of lung conditions induced by therapeutic interventions
- those changes are plausible and correspond to the information that an experienced user would expect based on his knowledge about lung physiology

Please respond the following questions in eCRF if this does not interfere with your clinical routine.

1. Select the view „**Main**".
   Does the **Tidal Image** indicate poorly or non-ventilated lung regions and does this location approximately match with those regions, where CXR or lung CT shows either lung collapse, atelectasis or pleura effusion?

2. Select the view **"Main"** and observe the Tidal Image, while one of the lungs is blocked.
   Does the **Tidal Image correctly** indicate which side of the lung is not being ventilated?

3. Open the view **"dEELI trend"** after the PEEP setting has been changed. Set C1 at the lower and C2 at the higher PEEP level.
   Does the image dEELI: C2 minus C1 show the expected increase of endexp.lung volume in turquoise (light blue) color?

4. Open the view **"End-insp. trend"** after the PEEP setting has been changed significantly (2 mbar or more). Set C1 at the lower and C2 at the higher PEEP level.
   Does the image Change: C2 minus C1 and/or the corresponding regional Tidal Variations show the expected redistribution of ventilation from ventral to dorsal?

5. Open the view **"dEELI trend"** after lung suction has been conducted. Set C1 at a phase before and C2 during or immediately after the lung suction.
   Does the image dEELI: C2 minus C1 show the expected decrease of lung volume in orange color?

6. Select the view **"Main"** and observe the Tidal Image from a patient with pneumonectomy.
   Does the Tidal Image properly indicate the non-ventilated lung regions and does the location approximately match with those region, where the lung has been removed?