Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	**LIFEGUARD Study** – Continuous Respiratory Monitoring on the General Ward
Clinical Investigation Plan Identifier	MDT17026
Study Product Name	• Capnostream™ 20p and its accessories, including any sensor for SpO_2 measurements and filter line for $etCO_2$ sampling. • Vital Sync™ Virtual Patient Monitoring Platform • PM1000N-RR Nellcor™ Bedside Respiratory Patient Monitoring System and its accessories, including any sensor for SpO_2 measurements.
Sponsor	[redacted]
Authorized Representative	[redacted]
Document Version	2.0 June 19, 2019
Principal Investigators	[redacted]

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1. Glossary

Term	Abbreviation	Definition
Adverse Event	AE	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the investigational medical device. NOTE 1 This definition includes events related to the investigational medical device or the comparator. NOTE 2 This definition includes events related to the procedures involved. NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect	ADE	Adverse event related to the use of an investigational medical device. NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Admit, Discharge, Transfer	ADT	Software application used by healthcare facilities to track patients from the point of arrival at a hospital until departure by transfer, discharge, or death.
American Society of Anesthesiologists physical status classification system	ASA PS	A surgical risk classification scale based upon health status assessment with range of ASA I - ASA VI.
Assess Respiratory Risk in Surgical Patients in Catalonia Score	ARISCAT Score	ARISCAT Score is an accurate risk score for predicting high or intermediate risk for postoperative pulmonary complications in patients undergoing surgery, calculated based on preoperative data such as on patient's age, preoperative SpO2, respiratory infection, anemia, surgery type and duration.
Capnography	CO_2 monitoring	A non-invasive method for monitoring the level of carbon dioxide in exhaled breath ($etCO_2$).

Term	Abbreviation	Definition
Clinical Investigation Plan	CIP	The present document describing LIFEGUARD Study Protocol.
Code Blue	Code Blue	An emergency situation in which a patient is in cardiopulmonary arrest, requiring a Rapid Response Team (see definition) to rush to the specific location and begin immediate resuscitative efforts.
Electronic Medical Records	EMR	A digital version of medical record that contains all of a patient's medical history in one practice.
Early Warning Score	EWS	Physiologic track and trigger systems, based on patients' vital signs, used to monitor adult patients in acute hospital settings to prevent Adverse Events.
Electronic Case Report Forms	eCRF	Forms where the clinical data are collected. eCRF is the electronic version of case report forms.
Ethical Committee	EC	Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human patients. The primary purpose of such review is to assure the protection of the rights and welfare of the human patients.
End Tidal CO_2	$etCO_2$	The numeric partial pressure of the maximum value of carbon dioxide in the exhaled breath over the last 20 seconds. The $etCO_2$ numeric value is updated once a second.
Intensive Care Unit	ICU	Acute care with 24 hour coverage. Patients may be directly transferred from the OR to the ICU or via the PACU.
Integrated Pulmonary Index™	IPI	The Integrated Pulmonary Index (IPI) is a composite index of $etCO_2$, SpO_2, RR and PR that is intended to indicate changes in physiological status as indicated by the monitored variables and cleared by FDA (K082268) in 2009.
Preoperative Score to Predict Postoperative Mortality Score	POSPOM Score	POSPOM Score is an accurate risk score for predicting in-hospital mortality in patients undergoing surgery, calculated based on preoperative data such as on patient's age, planned

Term	Abbreviation	Definition
		surgery and presence of additional diseases or disorders.
Pulse Rate	PR	Pulsatile cycle in beats per minute via pulse oximeter technology.
Pulse Oximetry	SpO_2	Depends on pulsatile blood flow and measures only the oxyhemoglobin in arterial blood as it leaves the heart.
Rapid Response Team	RRT	A team of health care providers that responds to hospitalized patients with early signs of deterioration on non-intensive care units to prevent respiratory or cardiac arrest.
Respiratory Compromise	RC	Respiratory compromise consists of respiratory insufficiency, compromise, distress, arrest, and failure. Respiratory Compromise is a state in which there is a high likelihood of decompensation into respiratory insufficiency, respiratory failure or death, but in which specific interventions (enhanced monitoring and/or therapies) might prevent or mitigate decompensation.
Respiratory Depression	RD	Respiratory depression is a decrease in the effectiveness of an individual's ventilatory function generally defined as deviation of respiratory rate, pulse oximetry value or arterial carbon dioxide tension from an arbitrary threshold[1].
Remote Data Capture	RDC	An interface that allows site users at sites to enter data directly into the study database via a web interface. RDC is an example of Electronic Data Capture method or EDC.
Respiration Rate	RR	The count of breaths per minute based upon the carbon dioxide cycle as measured by capnography.
Serious Adverse Device Effect	SADE	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Serious Adverse Event	SAE	An adverse event that a) led to death,

Term	Abbreviation	Definition
		b) led to serious deterioration in the health of the patient, that either resulted in c) a life-threatening illness or injury, or d) a permanent impairment of a body structure or a body function, or e) in-patient or prolonged hospitalization, or f) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, g) led to fetal distress, fetal death or a congenital abnormality or birth defect.
Vital Sync™	VS	Vital Sync™ is the brand under which all Integrated Patient Intelligence related products are sold. Included in the brand are the Vital Sync Informatics Manager (VSIM) and the Vital Sync Virtual Patient Monitoring Platform (VPMP).
Vital Sync™ Informatics Manager	VSIM	Is a software solution that resides on a hospitals network that collects, organizes, redistributes, and stores medical device data and device diagnostic information from supported devices to the HIPPA compliant hospital Electronic Medical Record (EMR) and Clinical Information System (CIS).
Vital Sync™ Virtual Patient Monitoring Platform	Vital Sync™ VPMP	A remote continuous patient monitoring software solution allowing EMR, ADT and annunciation connectivity. It allows clinicians to remotely view patient information from multiple device categories (ventilators, capnography monitors, pulse oximeters, depth of consciousness monitors and regional oximetry) on any web-enabled device (smartphones, tablets, desktops, central nurse station).
Vulnerable patient		Individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

Term	Abbreviation	Definition
		EXAMPLE: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable patients include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention. This might also include pregnant, parturient or breastfeeding patients and patients hospitalized without their consent.

2. Synopsis

Title	**LIFEGUARD Study** – Continuous Respiratory Monitoring on the General Ward
Clinical Study Type	Prospective, interventional, post-market pilot study
Product Name	• Capnostream™ 20p and its accessories, including any sensor for SpO_2 measurements and filter line for $etCO_2$ sampling. • Vital Sync™ Virtual Patient Monitoring Platform • PM1000N-RR Nellcor™ Bedside Respiratory Patient Monitoring System and its accessories, including any sensor for SpO_2 measurements.
Sponsor	[redacted]
Authorized Representative	[redacted]
Investigation Purpose	The purpose of this study is to quantify the incidence and the severity of postoperative RC markers on high risk postsurgical patients on a general ward.
Product Status	Products used are commercially available (CE-Marked) and used within intended use in the participating countries.
Primary Objective(s)	The primary objective of this study is to quantify the incidence of RC markers in high risk postsurgical patients, using a system comprised of two continuous monitoring devices, connected to a remote monitoring platform. The occurrence of at least one of the following RC markers will be considered as primary endpoint for patients monitored by Capnostream 20p during both study Phases: 1. SpO2 ≤ 90% for ≥ 3 minutes. 2. RR ≤ 8 or ≥ 22 bpm for ≥ 3 minutes. 3. etCO2 ≤ 15 or ≥ 60 mmHg for ≥ 3 minutes. 4. Apnea episode lasting > 30 seconds.

	The occurrence of at least one of the following RC markers will be considered as primary endpoint for patients monitored by PM1000N-RR during both study Phases: 1. SpO2 ≤ 90% for ≥ 3 minutes. 2. RR ≤ 8 or ≥ 22 bpm for ≥ 3 minutes.
Secondary Objective(s)	The study secondary objectives are the following: • To compare the two study Phases in terms of primary endpoint incidence. • To compare the two study Phases in terms of respiratory AEs and SAE incidence, numbers of ICU transfers and related length of stay, Code blues and RRT responses. • To evaluate the impact of introducing continuous monitoring devices connected to a remote monitoring platform, on the clinical workflow, defined as the rate of clinical early interventions performed by nurse staff to prevent a potential AE (e.g. patient stimulation, Jaw thrust maneuver, oxygen administration started or increased, medication change, etc.). • To evaluate the impact of introducing continuous monitoring devices connected to a remote monitoring platform on clinical staff's workflow, defined as clinical staff's satisfaction related to the monitoring system. • To characterize the predictive values of etCO2, RR, SpO2, plethysmography-derived RR, IPI[2] and EWS in respect to respiratory AEs and other SAE. Related secondary endpoints are: • Incidence of RC markers recorded during each Phase. • Incidence of respiratory AEs and SAE, number of ICU transfers and related length of stay, Code blues and RRT responses recorded in the two study Phases. • Average rate of early interventions for patient will be calculated in both study Phases. In Phase I there should only be non- alarm-triggered interventions, as in clinical practice, while in Phase II there should be two sub-groups of clinical early interventions: alarm-triggered and non- alarm-triggered. • Clinical staff's satisfaction related to each of the monitoring systems introduction in their current workflow will be evaluated through a survey performed at the end of the study.

	• Sensitivity and specificity of each monitored parameter in predicting and identifying respiratory AEs and SAE will be calculated.
Study Design	LIFEGUARD is a prospective, two-center, two-phase pilot study. The study population consists of post-surgical patients of adult age on the hospital ward at high risk of developing respiratory and cardiovascular events. During the study Phase I, 70 patients will be 1:1 randomly allocated to Capnostream 20p monitoring system or to PM1000N-RR pulse oximeter monitoring system. In this first phase the alarms of both devices will be silenced and the screen information blinded, to establish a baseline for the incidence of respiratory events in continuously monitored high risk patients. After Phase I and before starting Phase II, each participating site will have a minimum of a 1-month period for familiarization with the unblinded devices, based on a pre-defined hospital protocol for alarm management and escalation policy. During the study Phase II, an additional 140 patients will be 1:1 randomly allocated to Capnostream 20p or to PM1000N-RR monitoring but the screen information will be visible at the bedside and through the Vital Sync™ remote patient monitoring system. The nursing staff will respond to device alarms based on a pre-defined alarm management policy.
Sample Size	Approximately 210 patients will be enrolled in 2 European centers. Each participating center may involve one or more wards in the study, based on its distribution of high-risk patients that may benefit from monitoring.
Inclusion/Exclusion Criteria	The following criteria must be met for inclusion in the study: 1. Non-cardiac post-surgical patients at high risk of developing respiratory and cardiovascular events based on both ARISCAT[3] and POSPOM[4] scores on the hospital ward. In particular, to be enrolled a patient must have: POSPOM score ≥ 24 (> 3 times the mortality average risk) OR ARISCAT score ≥ 26 (High or intermediate risk for postoperative pulmonary complications). 2. Adult age (≥18 year old). 3. Patient is able and willing to give informed consent. Exclusion criteria (any of the list below):

	1. Expected ward length of stay ≤24 hours. 2. Post-surgical patients with American Society of Anesthesiologists physical status (ASA PS) V or higher. 3. Ventilated or intubated patients on the ward. 4. Patient is unwilling or unable to comply fully with study procedures (including non-toleration of the capnography cannula or skin contact allergies to medical grade adhesives) due to any disease condition which can raise doubt about compliance and influencing the study outcome. 5. Patient is a member of a vulnerable population, including legal incapacity or evidence that a patient cannot understand the purpose and risks of the study, regardless of authorized representative support. 6. Patient is participating in another potentially confounding drug or device clinical study.
Study Procedures and Assessments	Screening will be conducted to identify potential patients who will be admitted to the wards. If the patient is potentially eligible, fully informed and willing to consider participation, written informed consent must be obtained. A review of patient medical files by the investigator is required to determine preliminary eligibility according to patient inclusion and exclusion criteria. Patients are considered a screen failure if inclusion/exclusion criteria are not met prior to commencement of monitoring on the hospital ward. During both study phases, each patient will be monitored for a minimum of 24 hours and up to patient's mobilization or for a maximum of 72 hours. The continuous monitoring data will be recorded for subsequent analysis in conjunction with patient eCRFs. A regular check during the monitoring period should be completed to ensure the etCO2 filter line and SpO2 sensors are appropriately fitted on the patient. A survey will be conducted amongst the participating clinical staff to assess levels of their satisfaction and patient compliance with the different monitoring technologies and the overall feasibility of continuous respiratory monitoring in a general ward setting.
Safety Assessments	Occurrence of any AE with an underlying respiratory cause, SAE or Device Deficiencies will be documented.
Statistics	The sample size calculation is based on the primary endpoint and it was estimated using data from previous studies with a precision-based calculation.

	The analysis of primary objective will be based on the proportion of patients with at least one RC marker; it will be reported together with their 95% confidence intervals and separately for each arm and phase of the study. When comparison of clinical primary outcomes is conducted the propensity score methods could be used to control for biases and confounding which may occur due to the nature of this study. For all secondary outcomes the logistic regression model will be used to check potential predictors. Bivariate odds ratios (ORs) and 95% confidence intervals (95% CIs) will be estimated for each predictor. A multivariate logistic regression model will be performed according to univariate model's results. Other secondary outcomes will be performed using sensitivity and specificity analysis.

3. Introduction

3.1. Background

Early postsurgical period is associated with high incidence of postoperative pulmonary complications, including pneumonia, aspiration pneumonitis, respiratory failure, re-intubation within 48h, weaning failure, pleural effusion, atelectasis, bronchospasm, and pneumothorax[5]. The reported incidence rates range from 2 to 40% depending on context[5]. Estimates suggest that more than 1 million postoperative pulmonary complications occur annually in the United States, with 46, 200 related deaths and 4.8 million additional hospitalization days[3,6]. ISOS and EUSOS studies showed that in Europe the incidence of postsurgical critical events and in-hospital mortality are also significant[7,8].

Patients with one or more pulmonary complications, even mild, have up to 48% increased early postoperative mortality and up to 91% increased intensive care unit (ICU) admission[3,5,6]. In the case of postoperative pulmonary complications, a mean increase of hospital length of stay of approximately 8 days and a cost of surgery from 2 to 12-fold higher were also reported[5].

The most frequent severe postoperative respiratory complication is respiratory failure, defined as unexpected tracheal re-intubation, need for postoperative mechanical ventilation, postoperative acute lung injury and acute respiratory distress syndrome, with a reported incidence ranging between 0.2 and 3.4%[9]. Main predictive risk factors for hypoventilatory respiratory failure are obesity, breathing disorder conditions (e.g., obstructive sleep apnea), and postsurgical use of anesthetic and analgesic medications[10]. Respiratory failure is reported to contribute to increased hospital stay, cost of care and 30-days readmission rate[11–13].

Different scores have been developed to try predicting postoperative respiratory complications and mortality[3,14–16]. Main reported predictors include (but are not limited to) older age, preoperative low SpO2, previous respiratory infections, preoperative anemia, intrathoracic/upper abdominal surgical incision, concomitant cardiac disease, diabetes, surgery duration and emergency procedure[3].

Postoperative hypoxemia it is a strong indicator of patient instability, compromises wound healing and promotes other serious complications, including brain dysfunction, dysrhythmias and myocardial ischemia[17]. Prolonged hypoxemic episodes have been reported to be common in hospitalized patients recovering from non-cardiac surgery: up to 37% of patients had at least one episode of oxygen saturation < 90% lasting more than one hour while 3% had saturations <80% for at least 30 minutes[17].

Postsurgical patients at-risk of developing cardiopulmonary complications could benefit from both preventive interventions and more intensive postsurgical monitoring[5]. Up to 84% of in-hospital cardiopulmonary arrest events are preceded by prolonged periods of physiological and clinical instability[18,19]. Early intervention of clinically unstable patients by a medical emergency team significantly reduces the incidence of, and mortality from, unexpected cardiac arrest in hospital[20]. A significant decrease in the number of cases of respiratory failure, stroke, severe sepsis, and acute renal failure was also shown after the implementation of a medical emergency team in an Australian study[21]. In 2007, the UK National Institute for Health and Clinical Excellence recommended the use of physiological track and trigger systems to monitor adult patients in acute hospital settings: these systems, also known as Early Warning Scores (EWS), are based on the monitoring of patients' basic physiological observations such as pulse rate, SpO2, blood pressure, respiration rate, temperature and conscious level and are used to identify patients at risk of respiratory failure, cardiac arrest and death[22,23]. A systematic review has reported that EWS have a strong predictive value for the occurrence of cardiac arrest and death within 48 hours of measurement[24]. EWS has been demonstrated to be effective in predicting clinical deterioration that may lead to a cardiac arrest also in patients in wards that are poorly equipped to detect rapid patient deterioration[25]. National EWS (NEWS), based upon common vital signs such as temperature, respiratory rate, heart rate, systolic blood pressure, nursing assessments of consciousness level of the patient, SpO2 and use of supplemental oxygen is one of the most frequently utilized[24].

Respiratory compromise (RC) is a state in which there is a high likelihood of decompensation into respiratory depression, respiratory failure or death, but in which specific interventions (enhanced monitoring and/or therapies) might prevent or mitigate decompensation[26]. Patients with RC have up to a two-fold increase in mortality following delayed medical emergency team activation[27]. Detecting a patient's declining RC status before progression to respiratory depression in patients continuously monitored in the general ward could allow earlier intervention, thus potentially decreasing adverse outcomes[28].

Due to possibly improved patient safety, continuous SpO2 and capnography monitoring combined with automated decision support tools to determine potential or established patient critical illness are starting to have an important role also outside ICU[29]. Current standard of care for respiratory monitoring of high risk hospital ward patients, such as those receiving opioid therapy, is intermittent documentation of SpO_2 value (e.g. spot checks performed at 4 to 6 hours intervals)[1,17]. Respiratory rate (RR) is often determined by clinician assessment though manual inaccurate respiration counts[28].

Growing evidence supports the use of capnography for earlier and more reliable warnings of potential RC in postoperative patients in the general ward, compared with pulse oximetry[30–33]. Capnography monitoring has also been associated with in-hospital mortality in emergency department patients with cardiac arrest and suspected sepsis across a range of disease severity[34,35].

There are no data on the real incidence and severity of potential RC markers and their correlation with cardiopulmonary or other complications in European postsurgical patients. A pilot study on this topic could be useful to collect information on the utility of continuous SpO2 and capnography monitoring in this setting and to develop future clinical evidence. This study may also provide the data needed to evaluate certain health-economic outcomes associated with introduction of continuous monitoring in the general ward setting.

3.2. Purpose

The main purpose of this study is to quantify the incidence and the severity of postoperative RC markers on high risk postsurgical patients on a general ward.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective and Endpoint

The primary objective of this study is to quantify the incidence of RC markers in high risk postsurgical patients, using a system comprised of two continuous monitoring devices, connected to a remote monitoring platform.

The occurrence of at least one of the following RC markers will be considered as primary endpoint for patients monitored by Capnostream 20p during both study Phases:

1. SpO2 ≤ 90% for ≥ 3 minutes.
2. RR ≤ 8 or ≥ 22 bpm for ≥ 3 minutes.
3. etCO2 ≤ 15 or ≥ 60 mmHg for ≥ 3 minutes.
4. Apnea episode lasting > 30 seconds.

The occurrence of at least one of the following RC markers will be considered as primary endpoint for patients monitored by PM1000N-RR during both study Phases:

1. SpO2 ≤ 90% for ≥ 3 minutes.
2. RR ≤ 8 or ≥ 22 bpm for ≥ 3 minutes.

4.1.2. Secondary Objectives and Endpoints

The study secondary objectives are the followings:

1. To compare the two study Phases (see Section 5) in terms of primary endpoint incidence.
2. To compare the two study Phases in terms of respiratory AEs and SAE incidence, number of ICU transfers and related length of stay, Code blues and RRT responses.
3. To evaluate the impact of introducing continuous monitoring devices connected to a remote monitoring platform on the clinical workflow, defined as the rate of clinical early interventions performed by nursing staff to prevent a potential AE (e.g. patient stimulation, Jaw thrust maneuver, oxygen administration started or increased, medication change, etc.).

4. To evaluate the impact of introducing continuous monitoring devices connected to a remote monitoring platform on clinical staff workflow, defined as clinical staffs' satisfaction related to the monitoring system.
5. To characterize the predictive values of etCO2, RR, SpO2, plethysmography-derived RR, IPI[2] and EWS in respect to respiratory AEs and other SAE.

Related secondary endpoints are:

1. Incidence of RC markers recorded by the monitoring system during each Phase.
2. Incidence of respiratory AEs and SAE, number of ICU transfers and related length of stay, Code blues and RRT responses recorded in the two study Phases.
3. Average rate of early interventions for patient will be calculated in both study Phases. In Phase I there should only be non- alarm-triggered interventions, as in clinical practice, while in Phase II there should be two sub-groups of clinical early interventions: alarm-triggered and non- alarm-triggered.
4. Clinical staff's satisfaction related to the monitoring system's introduction in their current workflow will be evaluated through a survey performed at the end of the study.
5. Sensitivity and specificity of each monitored parameter in predicting and identifying respiratory AEs and SAE will be calculated. EWS will be the only parameter not automatically collected by the monitoring system but manually collected.

5. Study Design

LIFEGUARD is a prospective, post-market interventional, pilot study. Approximately 210 patients will be enrolled in two European centers.

The study will consist of two phases. During both phases the patients will be 1:1 randomly allocated to Capnostream20p or to PM1000N-RR monitoring. The Capnostream 20p device provides data on etCO2, RR, SpO2, PR and IPI through an oral nasal cannula and a finger sensor, while PM1000N-RR provides SpO2, PR and RR derived from plethysmography through a single finger sensor. The aim of the random allocation is to have similar patient populations receiving monitoring with the two different devices.

During the study Phase I, 70 patients will be enrolled and the alarms of both devices will be silenced and the screen information blinded, to establish the incidence of respiratory events, as is the current clinical practice in which continuous monitoring is not employed. After Phase I and before the start of study Phase II, each participating site will have a minimum of one month to familiarize themselves with the unblinded device, using a pre-defined hospital protocol for alarm management and escalation policy.

During the study Phase II, an additional 140 patients will be enrolled; but in this phase the screen information will be available, and the nursing staff will be instructed to respond to both devices' alarms based on a pre-defined hospital protocol.

During both phases, each patient will be monitored for a minimum of 24 hours and up to patient's full mobilization or for a maximum of 72 hours. At the end of the monitoring period the patient will complete the study and will continue to be treated according to standard clinical practice. Figure 1 reports the study Flow-Chart.

A survey will be conducted at the end of the study amongst the participating physicians and nurses to assess levels of their satisfaction and patient compliance with the two different monitoring technologies and the overall feasibility of continuous respiratory monitoring in a general ward setting.

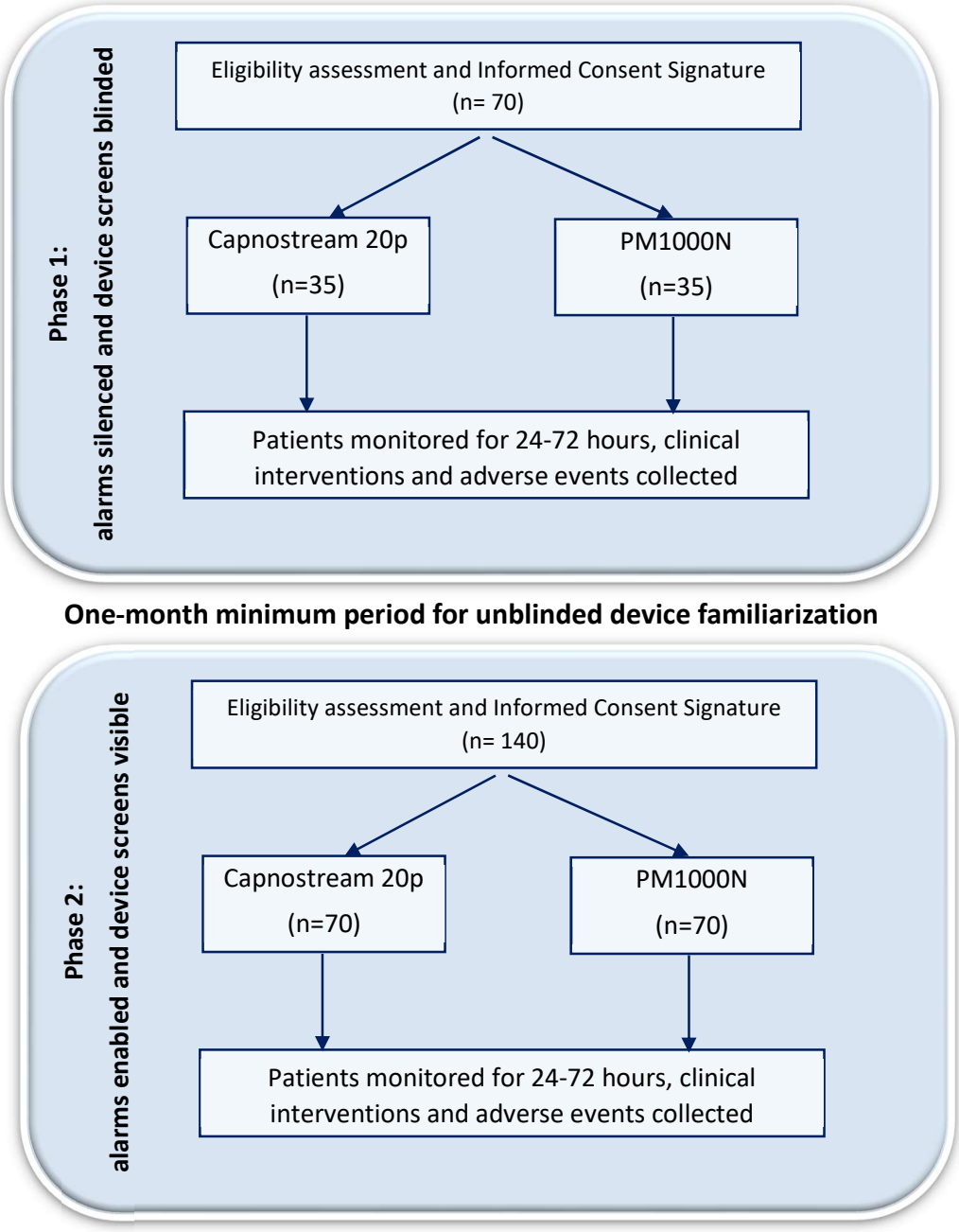
Capnography and pulse oximetry monitoring device data will be collected as well as clinical data related to respiratory compromise. Patients will be monitored per standard of care.

Enrollment at any single site will be limited to 50% (approximately 105 patients) to ensure poolability of the data across sites and reduce potential bias. Additional methods incorporated to minimize potential bias include the following:

- Systematic identification of potential patients via screening;
- Standard procedures and data collection requirements with a common electronic database for all sites;
- Random allocation to monitoring device.

Foreseeable factors that may compromise the outcome of the study include lack of enrollment or the lack of RC events.

Figure 1. Study Flow-chart.



5.1 Duration

Each patient will be in the study for a maximum period of 72 hours.

Each participating site may involve one or more wards, based on its distribution of surgical high-risk patients. The study is expected to last approximately one year.

5.2 Rationale

There are few data in the literature on the incidence of RC in high risk surgical patients continuously monitored on a general ward in Europe. This pilot study will collect data on a high number of patients monitored by capnographic and/or SpO2 monitoring, thus allowing quantification of the incidence of respiratory markers and their correlation with cardiopulmonary or other complications in clinical practice and the related clinical and workflow impact.

The study will also allow evaluation of two different monitoring devices coupled with a remote patient monitoring system in terms of sensitivity and patients' compliance.

6. Product Description

All devices used in this study are commercially available (CE-Marked) and used within intended use in Europe. The Instruction for Use (IFU) manual is provided with the product in local country language.

The Capnostream monitoring system includes a capnograph/pulse oximeter monitor, sampling line for end tidal carbon dioxide (etCO2), and pulse oximetry sensor for measuring the peripheral oxygen saturation of arterial hemoglobin (SpO2).

Table 1 provides a list of commercially available products that may be used in the study.

Table 1. Medtronic Market-Released Devices and Accessory Components

Model or Version	Product	Manufacturer
CS08651-02	Capnostream™ 20p Portable Bedside Monitor Capnograph/Pulse Oximeter	Oridion Medical
Version 1.1	Capnostream Software	
Vital Sync™ 2.4 or future CE-marked available versions	Vital Sync™ Virtual Patient Monitoring Platform	Medtronic
Smart CapnoLine H Plus Smart CapnoLine H CapnoLine H CapnoLine H 0_2 Smart CapnoLine Plus Smart CapnoLine O_2/CO_2 Nasal FilterLine	$etCO_2$ Sampling Line for Microstream™ – enabled capnography monitors (mono use)	Oridion Medical
PM1000N-RR	Nellcor™ Bedside Respiratory Patient Monitoring System Pulse Oximeter, with Nellcor™ Respiration Rate (RR) parameter; intended for the continuous, non-invasive monitoring of respiration rate.	Covidien llc.
OxiMax Max-A OxiMax Max-AL OxiMax MaxN MaxFast SoftCare	Nellcor™ SpO_2 Sensor (mono use)	Covidien llc.
	Additional Accessories Roll Stand Assembly Vesa mounting plate Manfrotto clamp Power Supply kit (Main Electrical Power Cord with AC adapter) Battery Pack Extra battery / charger 3.15 Amp Type F fuses FilterLine Starter Kit Sensor extension cables (4, 8, or 10 feet) SpO_2 Sensor Pack	

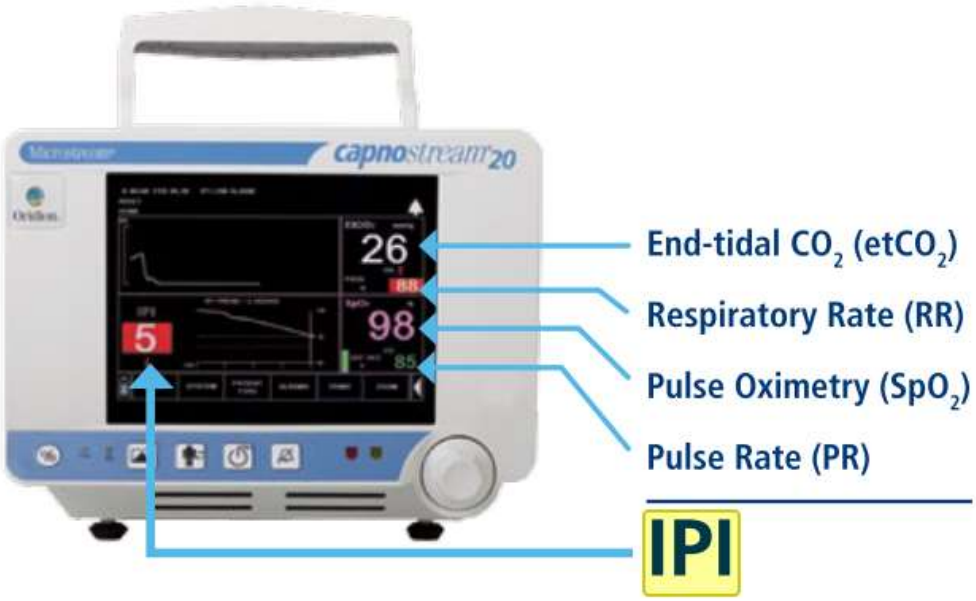
6.1. Capnostream Monitor

The Capnostream monitor and its accessories provide continuous, non-invasive measurement and monitoring of:

- End-tidal carbon dioxide ($etCO_2$) - level of carbon dioxide in exhaled breath.
- Respiratory rate (RR) – breaths per minute.
- Peripheral oxygen saturation of arterial hemoglobin (SpO_2)
- Pulse rate (PR) – pulsatile cycle in beats per minute via pulse oximeter technology

The device also provides an Integrated Pulmonary Index™ (henceforth referred to as IPI) value, which is a numerical value that integrates four major parameters measured by Capnostream in order to provide a simple indication of the patient's ventilatory status. The integrated parameters are $etCO_2$, RR, SpO_2, and PR. Only these four parameters are used to calculate IPI; other parameters are not taken into account.

Figure 2. Capnostream *20p* Portable Bedside Monitor

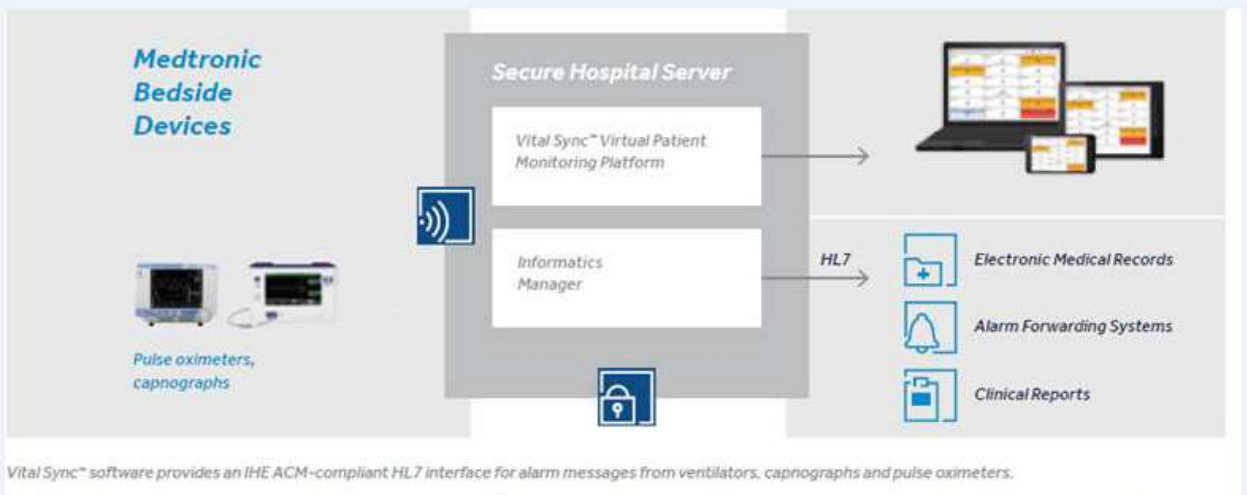


6.2. Vital Sync™

The Medtronic Vital Sync™ Informatics Manager & Virtual Patient Monitoring Platform is an FDA cleared and CE marked medical device. The Vital Sync™ Informatics Manager is the software that is intended to route and store medical device data and device diagnostic information from supported devices to the Electronic Medical Record (EMR) and Clinical Information System (CIS). The Vital Sync™ Virtual Patient Monitoring Platform is a remote monitoring platform that displays physiologic data, waveforms and alarms routed through the Vital Sync™ Informatics Manager for supported devices. The Capnostream 20p and PM1000N-RR are supported devices on this system. Patient information, generated during

Capnography and Pulse-Oximetry monitoring is transmitted wirelessly from the bedside devices to the hospital's server. The Vital Sync™ software, which can reside on hospital's server, takes this information and makes it viewable on any web-enabled device on the hospital network including a workstation or a Microsoft Surface tablet in case of nurse mobility. The information is formatted into HL7 protocol and written into the hospital EMR. HL7 protocol includes Electronic Medical Records, Alarm forwarding and Clinical Reports. The EMR integration feature of Vital Sync™ software will not be used in this study. No information can therefore be retrieved from the hospital EMR by the software. Patient data required for EWS calculation will be manually inputted to allow a retrospective analysis.
For the purpose of the clinical study, the CE marked Vital Sync™ Version 2.4 or future CE marked versions will be installed at the 2 sites using a dedicated server computer to be provided either by the site themselves, or by Medtronic.

Figure 3. Vital Sync™ VPMP

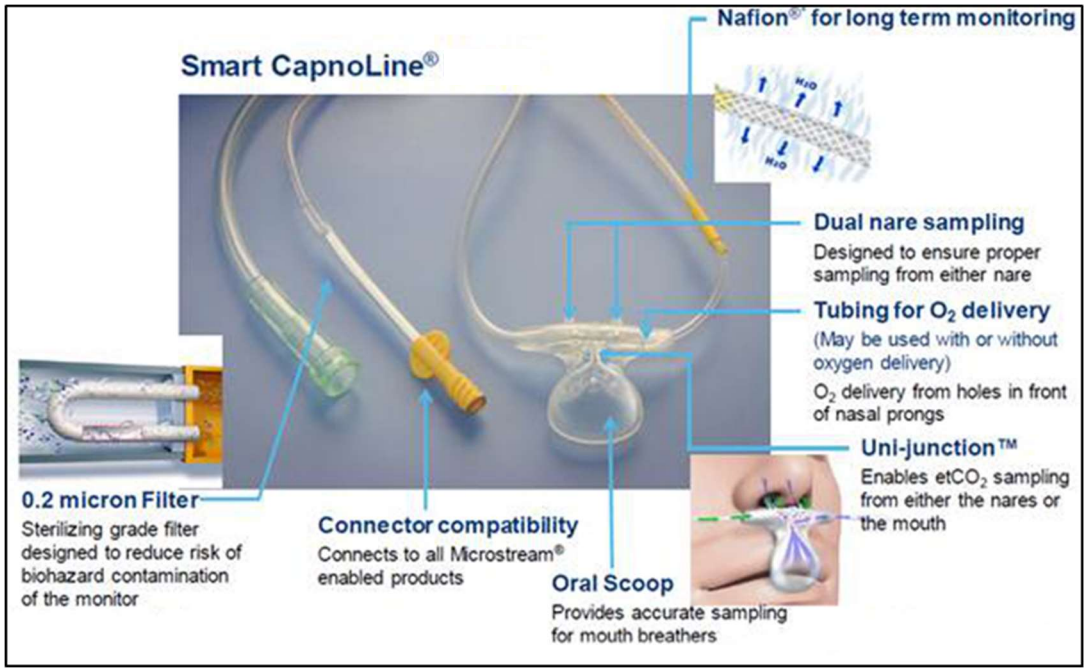


6.3. End-tidal Carbon Dioxide ($etCO_2$) Sampling Line

A sample of the exhaled gases are delivered from the patient (via a cannula) into the monitor for $etCO_2$ measurement. The $etCO_2$ sample line (also referred to as a filter line) is a disposable single use sampling line. Each study patient will be connected to the Capnostream monitor with an $etCO_2$ sampling line.

Supplemental oxygen may also be delivered through the sampling line, as needed. Any supplemental oxygen, up to 5 lit/min, will be delivered per usual clinical practice. The supplemental oxygen is not provided through the monitor.

Figure 4. $etCO_2$ Sampling Line



6.4. Nellcor™ Bedside SpO2 Patient Monitoring System

The Nellcor™ Bedside Respiratory Patient Monitoring System is a portable pulse oximeter intended for continuous non-invasive monitoring of:

- Peripheral oxygen saturation of arterial hemoglobin (SpO_2)
- Pulse rate (PR) – pulsatile cycle in beats per minute via pulse oximeter technology
- Respiratory rate (RR) – plethysmography-derived

If the monitoring system detects an alarm condition, it provides both visual and audible alarms.

Figure 5. Nellcor™ Bedside Respiratory Patient Monitoring System

6.5. Peripheral Oxygen Saturation (SpO_2) Sensor

Pulse oximetry is a non-invasive method of measuring the amount of hemoglobin saturated with oxygen or SpO_2. Light emitting diodes (LEDs) emit red and infrared light. Changes in light absorption during the pulsatile cycle determine the SpO_2.

The oxygen transducers (sensors) are available as a reusable or a disposable single use sensor.

Each study patient will be connected to the Nellcor or Capnostream monitor with a non-invasive SpO_2 disposable sensor applied to a finger (index finger preferred).

Figure 6. SpO_2 Sensor

6.6. Packaging

The devices used are all CE-Marked and will be provided with their standard packaging. Labelling of all the devices will be in local language.

6.7. Intended Population

The Capnostream™ 20p combined capnograph/pulse oximeter monitor and its accessories are intended to provide professionally trained health care providers with continuous, non-invasive measurement and monitoring of carbon dioxide concentration of the expired and inspired breath and respiration rate, and with continuous non-invasive monitoring of functional oxygen saturation of arterial hemoglobin (SpO2) and pulse rate. It is intended for use with neonatal, pediatric, and adult patients in hospitals, hospital-type facilities, and intra-hospital transport environments.

The Nellcor™ Bedside Respiratory Patient Monitoring System is a portable pulse oximeter intended for prescription use only as a continuous non-invasive monitor of arterial oxygen saturation (SpO2) and pulse rate of adult, pediatric, and neonatal patients during both no motion and motion conditions, and for patients who are well or poorly perfused. The monitoring system is intended for use in hospitals, hospital-type facilities, and during intra-hospital transport. The OxiMax SPD™ Alert (SPD) feature is intended only for facility-use care of adults to detect patterns of desaturation indicative of repetitive reductions in airflow through the upper airway and into the lungs.

6.8. Equipment

The participating site will receive at minimum the following study specific equipment:

- Two Capnostream monitors per site and accessories as described above in section 6.1
- Two PM1000N-RR monitors and accessories as described above in section 6.4
- Disposables for Capnostream and PM1000N-RR monitors, including etCO2 sampling lines and SpO2 sensors
- Vital Sync™ related equipment as described above in section 6.2
- As preferred by each site, a dedicated server may be provided to host the Vital Sync™ software
- Microsoft Surface tablets may be provided to hospital nurses for remote monitoring

Monitor's calibration information is provided in their respective manual. Any additional maintenance or cleaning procedures should follow the operator's institution guidelines.

6.9. Product Use

Disposition or use of product provided to the site by the study sponsor is for study patient use only.

6.10. Product Training Requirements

Product information will be included in the study training materials. A protocol for alarm management in Phase II, in agreement with hospital policy, will be developed and shared with nursing staff.

6.11. Product Receipt and Tracking

Medtronic will allow shipment of study devices prior to the Site Initiation Visit for training purposes only. Study devices should be used exclusively for patients enrolled in the study and can be used following official site activation from the Clinical Study Manager.

Participating sites will be provided with a sufficient number of Capnostream and Nellcor monitors. In addition, a sufficient number of etCO2 sample lines and SpO2 Sensors will be provided.

Single use products (see Table 1) will be provided initially to participating sites in line with the number of expected patients to be enrolled. All the study devices will be provided free of charge by the sponsor for the duration of the study and they should be used only in this clinical study according to the CIP. They may be directly shipped to the sites or through the Medtronic field representative.

The following records will be maintained by the site personnel at minimum for product delivery, receipt, use, disposal and return at each study center: dates, quantities, lot/serial numbers, patient ID, and expiration dates, as applicable.

6.12. Product Storage

Product provided to the site should be stored in a secured area with access limited to delegated study staff.

6.13. Product Return

Product provided to the site shall be returned at the end of the study (excludes consumable products that have been used during the course of the study). When returning the clinical study equipment the proper use of skids and pallets, as well as boxes or crates of the appropriate size and materials for their contents, will minimize damage to the equipment. Containers should be properly cushioned and braced for shock and vibration mitigation and adequately sealed and filled when possible with the weight evenly distributed.

Containers and inner pack material going out of the country should be used in conjunction with moisture-resistant material such as desiccant and barrier bags. Straps, seals and shrink wrapping help minimize pilferage of the equipment during transport.

6.14. Product Accountability

Reconciliation of product received, used, disposed and returned will be completed at the end of the study. Medtronic will perform periodic reconciliation of product to ensure traceability.

7. Selection of Patients

7.1 Study Population

The target study population consists of post-surgical patients of adult age at high risk of developing respiratory and cardiovascular events on the hospital ward.

7.2 Patient Enrollment

A patient is considered enrolled in the study once he/she signs the Informed Consent form and meets the inclusion/exclusion criteria.

The investigator will maintain a log of all patients enrolled in the clinical investigation. A Patient Identification and Enrollment Log is a document to keep a confidential list of names of all patients participating in the clinical study.

7.3 Inclusion Criteria

- Non-cardiac post-surgical patients at high risk of developing respiratory and cardiovascular events based on both ARISCAT[3] and POSPOM[4] scores.
  ARISCAT Score is an accurate risk score for predicting high or intermediate risk for postoperative pulmonary complications in patients undergoing surgery, calculated based on preoperative data such as on patient's age, preoperative SpO_2, respiratory infection, anaemia, surgery type and duration[3].

  POSPOM Score is an accurate risk score for predicting in-hospital mortality in patients undergoing surgery, calculated based on preoperative data such as on patient's age, planned surgery and presence of additional diseases or disorders[4] .

  In particular, to be enrolled a patient must have:

  POSPOM score ≥ 24 (> 3 times the mortality average risk);

  OR

  ARISCAT score ≥ 26 (High or intermediate risk for postoperative pulmonary complications).

- Adult age (≥18 year old).
- Patient is able and willing to give informed consent.

7.4 Exclusion Criteria

1. Expected ward length of stay ≤24 hours.
2. Post-surgical patients with American Society of Anesthesiologists physical status (ASA PS) V or higher.
3. Ventilated or intubated patients.
4. Patient is unwilling or unable to comply fully with study procedures (including non-toleration of the capnography cannula or skin contact allergies to medical grade adhesives) due to any disease condition which can raise doubt about compliance and influencing the study outcome.
5. Patient is a member of a vulnerable population, including legal incapacity or evidence that a patient cannot understand the purpose and risks of the study, regardless of authorized representative support.
6. Patient is participating in another potentially confounding drug or device clinical study.

8. Study Procedures

8.1 Schedule of Events

Data will be collected for Screening, Enrollment Visit and Monitoring Period. Additional data will be collected for Adverse Events, Device Deficiencies and Protocol Deviations.

Data collection requirements are summarized in Table 2. The study site personnel must report all study specific Adverse Events and changes in status of these Adverse Events from time of enrollment until a patient exits the study.

Table 2. Data Collection Requirements

Data	Screening Evaluation	Enrollment	Monitoring	Study Exit	Survey (at the study end)
Informed Consent	X				
Inclusion/Exclusion Criteria Evaluation	X				
Medical History		X			
Demographic & Physical Examination		X			
Vital Signs		X	X		
Supplemental Oxygen Use		X	X		
Surgery Information		X			
Monitoring Duration			X		
Medications		X	X		
Number/type of staff interventions (alarm and non-related)			X		
Adverse Events		X	X	X	
Device Memory Data			X		
Patients' compliance			X		
Product Information			X		
Device Deficiencies			X	X	
Protocol Deviations	X	X	X	X	
Reason for Study Exit				X	
Date of Patient Discharge from Hospital				X	
Clinical staff's satisfaction and workflow impact					X

8.2 Patient Screening

A consideration of all potential patients is recommended to minimize selection bias. All potential patients, whether finally enrolled in the study or not, will be entered on the Screening Log.

If the patient is potentially eligible and willing to consider participation, written informed consent must be obtained. A review of patient's files by the investigator is required to determine preliminary eligibility according to inclusion and exclusion criteria. Information included on the Screening Log includes:

- Informed consent signature date, if applicable
- Inclusion / exclusion criteria evaluation

Patients will be considered a screen failure and immediately exited from the study if the patient signs the Informed Consent but fails to meet study inclusion/exclusion criteria prior to monitoring on the hospital ward. The reason for screen failure will be documented on the Screening Log. Premature exit from the study by a patient must be documented on the Study Exit eCRF.

8.3 Prior and Concomitant Medications

Medications relevant to the study (see Appendix C) will be listed in the eCRF. Details of relevant medications used during surgery and recovery will be collected at study enrollment and during the monitoring period. Medications will be administered to patients during the study according to hospital policy.

8.4 Patient Consent

The investigator or authorized designee must obtain written informed consent before any clinical study related activity takes place. Written informed consent must be obtained prior to surgery.

In advance of the consent discussion, the patient should receive the EC approved Patient Information and Informed Consent Form. During the consent discussion, the investigator or his/her authorized designee must fully inform the patient of all aspects of the clinical study that are relevant to the patient's decision to participate in the clinical study. If a patient is illiterate, an impartial witness must be present during the entire informed consent discussion. All items addressed in the Patient Information and the Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the patient and the impartial witness, where applicable.

The patient must have ample time and opportunity to read and understand the Patient Information and the Informed Consent Form, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the patient.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a patient to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the patient's rights.

When the patient decides to participate in the clinical study, the Informed Consent Form must be signed and personally dated by the patient and investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Patient Information and Informed Consent Form was accurately explained and clearly understood by the

patient, and that informed consent was freely given. Detailed documentation of the process must be recorded in the patient's case history.

After all persons have signed and dated the Informed Consent Form, the investigator must provide the patient with a copy of the Patient Information and the Informed Consent Form.

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the patient in a timely manner.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the patient's confirmed participation in the clinical study. The revised information will be sent for approval by the EC. After approval by the EC, a copy of this information must be provided to the any patients that are still participating in the study and re-consent obtained if requested by the EC.

8.5 Enrollment

The point of enrollment is completion of informed consent and confirmation of inclusion/exclusion criteria per the screening evaluation.

Data collected for enrolled patients includes:

- Medical history (including surgical, apnea, and medical therapy such as oxygen use and opioid use)
- Demographic & Physical exam
- Vital signs
- Supplemental oxygen use
- Surgery information

8.6 Treatment Assignment

Patients will be randomly allocated 1:1 to either Capnostream™ 20p or Nellcor Monitoring Systems both in Phase I and in Phase II. The device allocation will be unblinded to both patient and physician.

The sequence of treatments will be randomly permuted in blocks of 2 or 4 patients per block. The blocked randomization will be centralized and schedules will be created by the study statistician using statistical software. The randomization will be performed by the center via the EDC system (Oracle Clinical). To minimize the selection bias, the randomization procedure will be unpredictable. In this study a center stratified blocked randomization will be used, so that a separate permuted block randomization will be performed for each center. This guarantees treatment balance within strata.

8.7 Monitoring Period

Continuous monitoring from either Capnostream™ 20p or Nellcor Monitoring Systems will be performed on all patients for a minimum of 24 hours. The monitoring period will last up to patient's full mobilization or up to a maximum of 72 hours, if the patient is still bed-ridden after two days post-surgery.

The monitoring period will start for patients once they arrive on the ward. For patients who are determined to be at high risk due to opioid therapy and not due to other pre-existing factors, monitoring of capnography and pulse oximeter data will start only after opioid therapy has been initiated.

Monitoring may be discontinued if the patient is discharged from the hospital ward.

During Phase I the alarm feature of the monitoring devices will be silenced and the screen information blinded. A regular check during the monitoring period should be completed to ensure the etCO2 filter line and SpO2 sensors are appropriately fitted on the patient.

During Phase II the medical staff will be instructed to respond to alarm feature of the monitoring devices and their screen will be open. A guideline will be created to instruct the nurses in responding to alarms and changes in the monitored parameters. An alarm will be considered a false positive by the observer if the SpO2 sensor or the etCO2 filter line is off the patient or misplaced. Alarms will be considered true positive if the SpO2 sensor and etCO2 filter line placement is correct: observations on patient activity and subsequent interventions will be recorded in the eCRF to identify clinically significant or insignificant alarmed events. As an example, patient activities such as talking, eating or gripping a book with the SpO2 sensor compressed will be marked as true positive with details of the activity recorded to identify the alarmed event as potentially clinically insignificant if no medical intervention was taken. The Monitoring eCRF will be completed to document:

- Care pathway (location/transfer within hospital)
- Alarm threshold applied to the monitor (to be collected during the Monitoring Phase II only for each measured parameter, PR, RR, SpO2 and EtO2).
- Systolic blood pressure and level of consciousness using the AVPU scale to allow the retrospective NEWS analysis
- Monitoring duration
- Vital signs
- Supplemental oxygen use
- Medications
- Product information
- Alarm classification by the study nurses (clinically significant or insignificant)
- Action taken in reaction to device alarm feature
- Adverse Events (as described in Section 10.2)

8.8 Study Exit

Once the monitoring period has ended the patient will be treated according to the hospital clinical practice. The patient will exit the study upon their discharge from the hospital. Any adverse events (as defined in section 10) observed between the end of the monitoring period and study exit are reportable (as described in section 10.2). The Study Exit eCRF will be used to document that the patient has exited from the study. The reason for study exit will be captured on the Study Exit eCRF. The date of study exit, which should correspond to the date of discharge from the hospital will also be captured here.

If the study exit was for any reason other than normal study completion, refer to section 8.12 of the CIP, for appropriate Study Exit eCRF completion.

8.9 Assessment of Safety

Methods and timing for assessing, recording, and analyzing safety parameters, including adverse events are described in the Adverse Event section.

8.10 Recording Data

The investigator will clearly mark the clinical records to indicate that the patient is enrolled in this clinical study. The patient's medical records will be used as source documents. Worksheets may serve as source documentation in particular cases if a data field is not in the patient's medical record. Details will be specified in the Monitoring Plan and specific guidance will be provided depending on the site practice.

Capnostream™ 20p or Nellcor Monitoring Systems' device memory data will be the source for the number and duration of RC markers. Device memory data will be exported to a flash memory device for each patient. The memory device will be stored at the investigation site. Device memory data will subsequently be downloaded and transferred to a secure server at Medtronic.

The device data transfer process will be tested and verified during the site initiation process. This will be completed to ensure data quality and identify any process improvements to maximize quality, as needed.

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents, such as patient medical records, must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, to be filed in the patient file. All baseline and medical history data must be derived from source documents.

Only authorized persons can complete eCRFs. Training will be provided to site personnel on the use of data collection tools. CRFs shall be electronically signed by investigators (physician) or by authorized site staff as specified on the Delegated Tasks List. The final version of eCRFs will be provided to the investigation sites when the investigational site has been declared ready for the study.

It is expected that eCRF will be completed within 15 days from the performed visit or as soon as source documents are available, except for Serious Adverse Events that require immediate reporting (see Table 3) and for Protocol Deviation requiring pre-approval. A delayed completion of the eCRF will not be considered a Protocol Deviation.

Sponsor study personnel will review all collected data and create data queries for missing data that impacts data analysis. Queries will be sent to the investigator or appropriate support staff for resolution.

Data reported on the eCRFs that are derived from source documents must be consistent with the source documents. Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

8.11 Deviation Handling

Deviations are instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. Intentional deviations are not permitted, except where necessary to protect the life or physical well-being of a patient in an emergency situation. All deviations must be documented and explained, regardless of the reason for the deviation. Deviations will be documented on the Protocol Deviation eCRF.

If circumstances permit, the principal investigator is required to obtain prior approval from Medtronic before initiating actions that are considered study deviations. Prior approval from EC or competent authority might also be needed if related to safety, well-being or integrity of scientific data. Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation and shall be reported.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the patient's interest. Such deviations from the CIP do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC, if applicable. Medtronic will inform the regulatory authorities, if required.

Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrollment or ultimately terminate the investigator's participation in the clinical study. Examples of serious investigator compliance issues that could determine site disqualification when repeated are:

- Failure to obtain and/or document informed consent;
- Inadequate device accountability;
- Failure to notify sponsor and or EC of reportable unanticipated adverse device effects, adverse events, device deficiencies, and/or adverse drug reactions within required timelines.

Medtronic is responsible for reviewing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.).

8.12 Patient Withdrawal or Discontinuation

If a patient is withdrawn from the clinical study, the reason for withdrawal shall be recorded on the Study Exit eCRF and in the patient's medical record.

Possible reasons for withdrawal from the study are:

- Adverse Event;
- Patient withdrew consent;
- Investigator withdrew patient from the study for medical reasons;
- Investigator withdrew patient from the study due to inclusion/exclusion criteria not met.

No patient follow-up is scheduled as per study design (excluding resolution of ongoing adverse events). Patients withdrawn for reasons other than screen failure will not be replaced.

Withdrawn patients will be treated according to standard clinical practice.

9. Risks and Benefits

9.1 Potential Risks

Devices used in this clinical study are commercially available and Medtronic is not aware of any concerns with these products. In the clinical study, the products will be used in accordance with their labeling, therefore no risks other than the risks typically associated with routine device use are anticipated.

Risks will be minimized by careful assessment by the patient's doctor prior to, during, and after the monitoring phase. In addition, apart from the monitoring, patients are treated according to general clinical practice, so no extra tests or follow-ups are required for the study. Therefore, no additional risks are associated with participation in this clinical study.

Possible risks associated with Capnostream™ 20p or Nellcor monitoring is mild to moderate skin irritation or discomfort (redness, itching, rash, pressure) associated with the pulse oximetry sensor or related to the application or removal of the sensor. The skin will be assessed before and after the application of the pulse oximetry sensors. Patients with known skin contact allergies to medical grade adhesives will not be recruited.

Possible risks associated only with Capnostream™ 20p is mild to moderate skin irritation or discomfort involved in wearing a filterline similar to a supplemental O_2 tube with an added oral scoop to collect a gas sample near the mouth for CO_2 analysis. The design mitigation to reduce skin allergic reactions is the use of latex free, ISO 10993 compliant components. Design of the oral/nasal interface and low pump suction pressure for sampling are means to reduce risk of discomfort.

9.2 Potential Benefits

Patients' participation in this study may offer no additional benefit in respect to the same treatments provided outside of the study.

Possible benefits for participating in this study include the following (although others are possible):

- Study patients may benefit from the structured, well-controlled clinical surveillance provided during the monitoring phase.
- The information gained from this study could result in the improved post-surgical management of other patients. Additionally, information collected from this study may assist in the design of a subsequent outcome study, the design of new product(s)/therap(y/ies) and/or instructions for use.

9.3 Risk-Benefit Rationale

Medtronic believes that the potential risks associated with the conduct of this study are minimal, using non-significant risk, non-invasive study devices for the following reasons:

- All the devices used in the study are commercially available and used within their intended use.
- Additional surveillance will be provided for close monitoring and recording of the patients' clinical status.

10. Adverse Events and Device Deficiencies

In this study the following AEs will be collected:

- All AEs with an underlying respiratory cause
- All SAEs
- All adverse device effects (ADE)

In addition, device deficiencies (DD) will be collected for this study.

RC markers will not be considered AE if the patient is asymptomatic and no actions are taken.

10.1 Definitions/Classifications

Definitions according to ISO 14155:2011 will be used in this study.

Where the definition indicates "device", it refers to any product used in the study. See product description section 6 for product information.

Table 3. Definition of Adverse Events and Device Deficiency

Term	Abbreviation	ISO Definition
Adverse Event	AE	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. *NOTE 1:* This definition includes events related to the investigational medical device or the comparator. *NOTE 2*: This definition includes events related to the procedures involved. *NOTE 3:* For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect	ADE	Adverse event related to the use of an investigational medical device. *NOTE 1:* This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. *NOTE 2:* This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Device Effect	SADE	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

Term	Abbreviation	ISO Definition
Serious Adverse Event	SAE	An adverse event that 1. led to death, 2. led to serious deterioration in the health of the subject, that either resulted in 3. resulted in a life-threatening illness or injury, or 4. resulted in a permanent impairment of a body structure or a body function, or 5. resulted in-patient or prolonged hospitalization, or 6. led to a medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, 7. led to fetal distress, fetal death or a congenital abnormality or birth defect. *NOTE:* Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Unanticipated Serious Adverse Device Effect	USADE	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. *NOTE:* Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency	DD	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE:* Device deficiencies include malfunctions, use errors, and inadequate labelling.

10.2 Reporting of Adverse Events

AE information will be collected throughout the study and reported to Medtronic on an AE eCRF, one for each adverse event. It is the responsibility of the investigator to identify the occurrence of adverse events to ensure that the information is accurately documented in the medical record and on the eCRFs.

Device Deficiency (DD) information will also be collected throughout the study and reported to Medtronic on a Device Deficiency eCRF. DDs require immediate reporting if they did not lead to an adverse event but could have led to a serious adverse device effect (SADE):

- if either suitable action had not been taken,
- if intervention had not been made, or
- if circumstances had been less fortunate

AE documentation will include the following information at a minimum:

- Date of event

- Time of the event
- Diagnosis and description (including confirmation of respiratory nature)
- Actions taken / treatment (including vital signs, and date and time of rescue related actions when applicable)
- Assessment of seriousness
- Relatedness to the event (including opioid therapy or device)
- Outcome or resolution and date of the resolution

For AEs that require immediate reporting, initial reporting may be done by phone, fax, e-mail, or preferably on the eCRF completing as much information as is available. The completed AE eCRF must be sent to Medtronic as soon as possible.

In case the investigator requires information from the sponsor in an emergency situation, the investigator can contact Technical Services or the Medtronic Study Manager. Contact information will be provided under separate cover.

The sponsor will ensure timely Adverse Event reporting to meet local regulatory requirements.

A list of anticipated adverse events that are expected in nature is included in Appendix A of this CIP.

Table 4. Reporting Requirements for Events

Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE):	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement.
EC	Submit to EC per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC	Submit to EC per local reporting requirement.
Serious Adverse Events (SAE)	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the event or of new information in relation with an already reported event.

Regulatory Authority	As per local reporting requirement.
EC	Submit to EC per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC	Submit to EC per local reporting requirement.
Adverse Device Effects (ADE)	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirement.
EC	Submit to EC per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC	Submit to EC per local reporting requirement.
All other AEs	
Investigator submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirement.
EC	Submit to EC per local reporting requirement.
Device Deficiency with SADE potential	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency.
Regulatory Authorities	As per local reporting requirement.
EC	As per local reporting requirement.
Sponsor submit to:	

Regulatory Authorities	As per local reporting requirement.
EC	As per local reporting requirement.
All other Device Deficiencies	
Investigator submit to	
Medtronic	Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory Authorities	As per local reporting requirement.
EC	As per local reporting requirement.

10.3 Patient deaths

All patient deaths and adverse events that lead to death must be reported by the investigator to Medtronic. Initial reporting may be done by phone, fax, e-mail, or preferably on the eCRF completing as much information as is available. The completed AE eCRF must be sent to Medtronic as soon as possible after the investigator first learns of the death.

10.4 Complaint reporting

A Product Complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

Market-released devices require product complaint reporting. The reporting of product complaints is not part of the clinical study and should be done via regular channels for product complaint reporting in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

11. Clinical Event Committee

This study will not have a Clinical Event Committee (CEC).

Since only two German sites will be involved, assessment of study specific endpoints and/or events will be performed by delegated site sub-Investigators that will perform cross-site events assessment

12. Statistical Design and Methods

12.1 Sample size justification

The sample size calculation is based on primary endpoint and it was estimated using data from previous studies with a precision-based calculation. Recent data on post-surgical patient have shown a proportion of patient with the RC markers for the SpO2 ≤ 85% for ≥ 3 minutes at 13%[17] and for RR ≤ 8 or ≥ 22 bpm

for ≥ 3 minutes at 1.4%[36] in patients undergoing opioid therapy. Using this information, a minimum proportion of 10% of patients with RC markers with a sample size of 260 patients will be able to obtain a 95% confidence level with a precision of 5% (ranging from 5% to 10%) and a power of at least 0.80 defined as the probability of achieving the desired precision. Considering a 10% withdrawal or potential dropouts and a potential attrition rate to monitoring compliance of 5% a total of approximately 210 patients will be enrolled. This cohort will be used prospectively for the blinded and not blinded phase with a ratio 1:2 respectively to minimize not blinded monitored patients. The blinded phase will enroll 70 patients randomly allocated 1:1 in the Capnostream 20p and PM1000N-RR arm while the not blinded phase will enroll 140 patients with same randomized schedule.

12.2 Data analysis and reporting

The data will be collected from each center in the eCRF data base via Oracle Clinical. A specific account number will be given to each center to access the system from any internet-enabled computer. Access to Internet is required for the sites to enter data into the system. User Identification codes will be created to identify data input from each center. The clinical data will be entered by the study staff and transmitted to the central database in an anonymous format so that the study sponsor will not be able to identify the patient, in accordance with the European Data Privacy Directive. Electronic automatic and manual queries will be generated for missing, incorrect or doubtful data and sent directly to the study center via Oracle Clinical. All the detailed data analyses are described in the Statistical Analysis Plan. Any deviations from this section and/or the Statistical Analysis Plan will be described and justified in the Final Clinical Study Report, as appropriate.

12.3 Analysis of clinical data

Patient demographics and baseline characteristics will be presented using appropriate summary statistics. This includes mean and standard deviation, minimum, maximum and median with the interquartile range [IQR] for continuous variables and counts and percentages for categorical variables. Summary statistics will be reported with maximum 2 decimals, as appropriate. The SAS software (SAS Institute Inc., Cary, NC, USA) will be used to perform statistical analyses. Statistical tests will be based on a two-sided significance level of 0.05. Graphical representations will be used as deemed appropriate. No adjustments for multiple comparisons or multiple look at data will be performed. Outliers and influential observations will be identified via graphical plots and according to study team decision the analysis could be repeated excluding potential outliers. In case of missing data, no imputation method will be implemented for analysis.

The Full Analysis Set (FAS) will be used for primary final analysis. Any patient who does not satisfying the inclusion/exclusion criteria will be eliminate from the FAS population. Details of endpoints analyses and additional analysis will be described in the Statistical Analysis Plan. The analyses of primary objective on the proportion of patient with at least one RC markers will be reported together with their 95% confidence intervals and separately for each arm and phase of the study (see primary endpoint definition). When comparison of clinical primary outcomes is conducted the propensity score methods could be used to control for biases and confounding which may be due to the nature of this study. The

difference between the two groups within phase and between phases within groups will be analyzed by means of unpaired t-test or Mann-Whitney test according to the normal or non-normal distribution. For one secondary outcome the logistic regression model will be used to check potential predictors. Bivariate odds ratios (ORs) and 95% confidence intervals (95% CIs) will be estimated for each predictor. A multivariate logistic regression model will be performed according to univariate model's results. Other secondary outcomes will be performed using sensitivity and specificity analysis.

13. Ethics

13.1 Statement(s) of Compliance

This clinical study will be conducted in compliance with the Declaration of Helsinki (2013), ISO 14155: 2011 and local laws and regulations, including data protection laws, the Clinical Trial Agreement, GCP and the CIP. All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, EC approval, clinical study training, clinical trial registration, risk-benefit assessment and publication policy. Adverse Event and Device Deficiency handling in the LIFEGUARD will be ISO 14155:2011 compliant, with the following exception: only those adverse events which are deemed to have an underlying respiratory cause, all Serious AEs, ADEs and DDs will be collected. Medtronic will prepare all the required regulatory authority documents and send them to the respective authority, if applicable.

The clinical study will not begin until EC and regulatory authority approvals, as appropriate, are received.

13.2 Ethics Committee

Prior to enrolling patients in this clinical study, each investigation site's EC will be required to approve the current Clinical Investigation Plan, the Patient Information and Informed Consent form, including any other written information to be provided to the patients and, if applicable, materials used to recruit patients. EC approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition, the approval letter needs to be accompanied by an EC roster or letter of compliance, to allow verification that the investigator, other investigation site personnel, and/or Medtronic personnel are not members of the EC. If they are members of the EC, written documentation is required stating that he/she did not participate in the approval process. If the EC imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the EC.

EC must inform Medtronic of any change in status of its approval once the investigational site has started enrollment. If any action is taken by an EC with respect to the investigation, that information will be sent directly to Medtronic who will immediately inform the investigator.

13.3 Regulatory Requirements / Competent Authorities

The study shall be conducted in accordance with the laws and regulations of the countries in which the clinical study is conducted, including data protection laws. In countries where submission to the regulatory authority is required per local law, no patients will be enrolled in the clinical study until the particular regulatory authority has approved the current Clinical Investigation Plan of the clinical study and other documents as required according to the local requirements. If the regulatory authority imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority.

13.4 Patient Compensation and Indemnification

While a fee will be provided to the participating centers for each enrolled patient, no additional fee/reimbursement will be provided to the patients.

This trial is conducted in Germany, therefore reimbursement and indemnification will be addressed on a country specific basis in the study documents and site Clinical Trial Agreements.

Patients are treated according to general clinical practice, so no extra tests or follow-ups are required and therefore no risks other than the risks typically associated with a routine device use are anticipated. If injuries happen, it will be treated in the same manner as per routine clinical practice. Costs of these treatments will be covered by the national health insurance (as applicable per country) as in usual clinical practice. The patient pays his/her co-payment for that treatment. No special compensation will be paid by the Sponsor.

14. Study Administration

14.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of the study per regulations. Appropriately trained Medtronic personnel or delegates appointed by Medtronic will perform study monitoring at the study center in order to ensure that the study is conducted in accordance with the Clinical Investigation Plan (CIP), the Clinical Trial Agreement, and applicable regulatory requirements. Medtronic must therefore be allowed access to the patient's clinic and hospital records when so requested as per the Patient Consent Form and Clinical Trial Agreement.

Frequency of monitoring visits will occur based on patient enrollment, duration of the study, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents (e.g., Informed Consent Form, EC approval letters and Clinical Trial Agreements, etc.) will be reviewed at each study center.

A Study Initiation Visit will be conducted after the EC approval and study agreement signature to train the investigational site. Interim Monitoring visits will be conducted to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to EC approval and review of the study, maintenance of records and reports, and review of source documents against patient eCRFs. Monitors facilitate site regulatory and study compliance by identifying findings of non-

compliance and communicating those findings along with recommendations for preventative/ corrective actions to site personnel. This may be done in collaboration with the study management and the local field personnel, if available. Communication with the site personnel occurs during the visit and following the visit via a written follow-up letter. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center. Study closure visits will be conducted via telephone or on site at each enrolling study center.

The Principal Investigator should be available during the Monitoring Visits or at least should be available to discuss by phone any eventual finding resulting from the Monitoring Visit.

14.2 Data Management

14.2.1 Patient Data

Patient data will be collected using the Remote Data Capture (RDC) management system. RDC is an interface that allows site users at sites to enter data directly into the study database via a web interface. RDC is an example of an Electronic Data Capture method (EDC).

RDC, developed by Oracle Clinical, utilizes electronic Case Report Forms (eCRFs). The application and data will be maintained on Medtronic servers. The system is a 21 CFR Part 11 compliant system which maintains an audit trail and change management system, including the original entry for comparison purposes.

Data will be reviewed using programmed and manual data checks. Data queries will be made available to centres for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be archived for the appropriate retention period. Following this period, Medtronic will only retain anonymized data and will delete any personal data.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

CRFs must be maintained and signed electronically within the electronic data capture system during the study.

14.2.2 Device Data

Device memory data will be exported to a flash memory device for each patient. The memory device will be stored at the investigation site. Device memory data will subsequently be downloaded and transferred to a secure server at Medtronic.

14.3 Direct Access to Source Data/Documents

14.3.1 Accessibility of Investigation Site Staff and Study Materials

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic Clinical Monitors and the Clinical Study Manager. This accessibility is of particular importance for reviewing data on the electronic Case Report Form (eCRF). Direct access to patient medical files for

source data verification (if applicable) will need to be granted and prepared prior to any monitoring visits.

14.3.2 Audits and Investigation Site Inspections

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities by personnel dependent of the employees involved in the clinical study. Regulatory authorities may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to Clinical Study Manager.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, EC review (if applicable), and regulatory inspections.

14.4 Confidentiality

All records and other information about patients participating in this study will be treated as confidential. The identity of a patient will never be disclosed in the event that study data are published.

Patient confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique patient identification code will be assigned and used to allow identification of all data reported for each patient.

Study data may be made available to third parties, e.g. in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the patient's privacy is guaranteed. Sites will maintain patient privacy according to local and national regulations and institutional requirements.

The confidentiality of data must be observed by all parties involved at all times throughout the study.

14.5 Liability

Covidien AG (represented in the European Union by Covidien Services Europe) is an indirect wholly owned subsidiary of Medtronic plc, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC.

14.6 CIP Amendments

Amendments to this Clinical Investigation Plan shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

The investigator may propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the EC, if applicable.

Administrative amendments to the Clinical Investigation Plan will be submitted to the EC and appropriate regulatory authorities for notification, if applicable.

14.7 Record Retention

14.7.1 Investigator Records

At a minimum, the following records must be kept by the investigator:

- Clinical Investigation Plan and, if applicable, any amendments
- Medtronic and EC approved Informed Consent
- Regulatory Authority approval or notification, if applicable
- Fully signed clinical trial agreement and confidentiality agreement (if not included in the clinical trial agreement)
- Financial disclosures
- Insurance certificates, if applicable
- Completed Delegated Task List and Curriculum Vitae of Primary Investigator
- Training documentation of all investigation site personnel
- Relevant communications
- Patient Identification and Enrollment Log Form
- Signed, dated and fully executed informed consent forms
- Fully executed eCRFs and corrections
- Copy of the Study Final Report

The investigator must retain the Investigator Site File, patient medical files and eCRF data in accordance with local law and regulations for a minimum period of 10 years after study completion.

The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

14.7.2 Sponsor Records

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Curriculum vitae of Primary investigators, Delegated Task Lists and training records of investigators and site staff
- EC approvals/notifications and regulatory approvals/notifications
- Signed Clinical Trial Agreements and signed agreements with third parties
- Insurance certificates, if applicable
- Medtronic and EC approved Informed Consents

- Site selection reports, site initiation reports and monitoring visit reports
- Adverse event reports
- Financial disclosures
- Fully executed eCRF data and corrections
- Device Memory data
- Study Final Report

14.8 Publication and Use of Information

The results of this clinical study will be submitted for publication. Publications and presentations referring to LIFEGUARD study will be coordinated by Medtronic to allow the use of all available data.

The study will be recorded on www.clinicaltrials.gov before the first enrollment.

The following publication policy will have to be adhered to by all participating investigation sites.

Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal. Names of all participating investigators will appear in the Acknowledgment of the paper.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for any lawful purposes, including marketing purposes, further research and development of devices or educational use, in compliance with applicable data privacy regulations.

The study sponsor will collect only pseudonymized data, and monitor study records.

Participating patients will not be identified in any published reports about the clinical study.

14.9 Suspension or Early Termination

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the clinical study.

If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC and the study patients or their legal representative.

Medtronic, EC or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of non-compliance to the CIP or lack of enrollment). If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. Medtronic shall then promptly inform the reviewing EC, if required, the study patients or their legal representative.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the

clinical study in the respective investigation site and immediately inform the sponsor and EC, if applicable.

In case of early investigation site suspension or termination patients will be followed-up as per standard of care.

In case of close out, the investigators will be notified and notification/report to EC and Regulatory Authority will be done, if required.

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16. Appendices

Appendix A: List of Anticipated Adverse Events

In Table 5 a list of possible respiratory related adverse events occurring in high risk post-surgical patients is reported.

In Table 6 a list of device related adverse events that may be possibly caused by the use of the devices required by this protocol is reported.

Note that occurrence of RC markers alone, if patient is asymptomatic and no invasive actions are taken, are not considered as adverse events but would meet the primary endpoint definition.

Table 5. Anticipated Respiratory Adverse Events

Partial airway obstruction that required an NMBA antagonist
Respiratory Insufficiency that would require Non-invasive positive pressure ventilation, ambu bag mask assisted ventilation
Respiratory failure that would require Invasive mechanical ventilation
Upper airway obstruction requiring airway support measures (oral or nasal) such as intubation or Laryngeal Mask Airway
Respiratory insufficiency/failure that would require a transfer to the ICU
Cardiopulmonary arrest
Death due to respiratory/pulmonary related complications

Table 6. Anticipated Device Related Adverse Events

AE	Definition	Mitigation
Minor to moderate discomfort at finger sensor site or oral/nasal cannula site	Minor to moderate discomfort/pain may be associated with application, presence or removal of study related sensors, or reaction to the standard adhesive with local irritation and redness or discomfort/pain related to sensor retention mechanism.	The skin will be assessed before and after the application of the pulse oximetry sensors and nasal cannula site. The design mitigation to reduce skin allergic reactions is the use of latex free, ISO 10993 compliant components. Design of the oral/nasal interface and low pump suction pressure for sampling are means to reduce risk of discomfort.
Itching (pruritus)	An abnormal sensation felt on the skin in a particular area.	
Pain (discomfort)	Subjective feeling of localized pain/discomfort	
Allergic reaction	An abnormal reaction of the body to a substance, as acute onset of skin rash or erythema.	The skin will be assessed before and after the application of the pulse oximetry sensors and nasal cannula site. Patients

AE	Definition	Mitigation
		with known skin contact allergies to medical grade adhesives will not be recruited.

Appendix B: Alarm Management Protocol

In the event of potential RC episodes, the nurse must assess the patient and identify the appropriate set of actions based on the patient's condition.

Criteria for notifying the patient's physician or a respiratory therapist, decreasing or stopping the patient's medication, administering a reversal agent, and/or using supplemental oxygen must be established by the hospital clinical team and included in the training protocol prior to the capnography monitoring implementation. Training must be provided to all nurses on the involved units, as well as respiratory therapists and rapid response nurses. The focus of education and training should include the significant clinical differences between monitoring a patient's oxygenation (via pulse oximetry) and monitoring ventilation (via capnography).

Recommended alarms setting during Study Phase II

To facilitate the detection of RC episodes, the following alarm setting could be programmed at the beginning of the Study Phase II:

Event	Alarm threshold
Low Respiration Rate	≤ 8 bpm (>30 sec)
High Respiration Rate	≥ 22 bpm (>30 sec)
SpO2 /Hypoxemia	≤ 90% (>30 sec)
Low EtCO2	≤ 15 mmHg (>30 sec)
High EtCO2	≥ 60 mmHg (>30 sec)
Apnea	Apnea > 30 sec
IPI	IPI ≤ 3 > 30 sec

Each site will be free to modify the alarms setting according to specific patients' needs or to decrease alarm-related burden.

Alarm response and escalation policy

Figure 1 provides an example of algorithm for responding to a respiratory monitor alarm. This could be used as starting draft if the site doesn't have its own protocol. Threshold for escalation should also be defined by each site.

There are different steps to be followed.

1. **Assess Patient:**

The bedside caregivers must be trained in reading respiratory monitored data and attentive to the respiratory warning signs.

- When the alarm sounds, first assess if the patient is breathing.

1a) Is Patient arousable?

Try to arouse the patient using the following methods:

- Call patient's name while stimulating him/her, such as shake shoulders, move arm, etc.
- Apply nail bed pressure.
- Perform a sternal rub.

Is patient breathing?

No: If the patient cannot be aroused, check if the patient is breathing. If the patient is not breathing, call Code *immediately*.

Yes: If the patient is arousable and breathing, assess the patient's breathing:

- Evaluate the patient's breathing data (respiratory rate, quality, rhythm, and depth) over time to identify any gradual increase or decrease in respiratory rate, EtCO2 waveforms, and/or SpO2 results.
- Assess the patient's EtCO2 data with other patient data, such as medications, vital signs, etc.
- Think critically of what the numbers reflect the patient's overall respiratory status.
- Evaluate any continuous IV infusion to rule out medication error.
- Check pump programming.
- Perform IV line reconciliation.

1b) Is Patient Breathing Effectively?

Yes: If patient is breathing effectively, re-assess patient per protocol.

No: Call Rapid Response Team immediately and then:

- Contact provider (and keep informed).
- Consult respiratory care practitioner.
- Check medications.

  Consider obtaining arterial blood gas.
- Consider administering reversal agent.
- Consider referral to a higher level of care.
- Consider initiating supplemental oxygen (*and jointly provide an intervention to support ventilation*).

2. Is Alarm Valid?

Yes: Go to Step 3

No: If the alarm appears to be invalid, troubleshoot equipment:

- Fix/confirm correct placement of cannula and sensors on the patient.
- Analyze waveforms for irregularities.
- Check alarm parameters are appropriate for the patient.

  Check for improper tube placement or equipment malfunction.

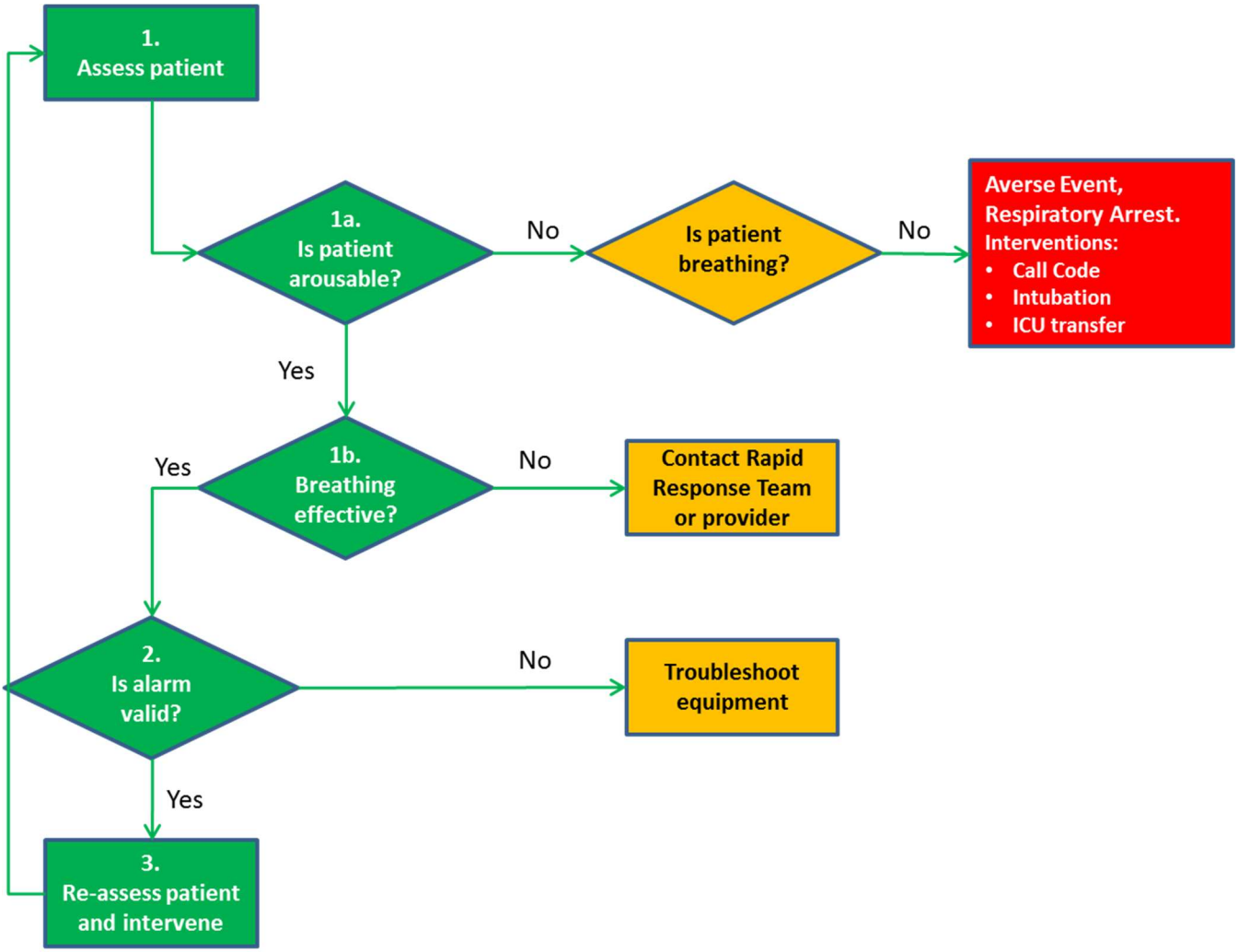
3. Re-Assess Patient and Intervene (per Protocol)

Regularly, re-assess patient (*see* Step #1 in Figure 1) and:

- Assess the patient's respiratory rate, quality, rhythm, and depth for any early signs of hypoventilation.

- Assess the patient's vital signs trends for any indication of decompensation.
- Assess the patient's pain and level of sedation, and consider adjusting opioid dose and/or frequency.
- Evaluate for Obstructive Sleep Apnea/sleep disorder.
- Consider obtaining authorization to initiate Non-invasive ventilation procedures, if needed.

Figure 1. Respiratory Monitoring Alarm Response Algorithm.



Appendix C: List of Medications

1.0 Medications		
1.1 Non-Opioid Analgesics ☐ Nonsteroidal Anti-Inflammatory Drugs ☐ COX-2 inhibitors ☐ Tramadol ☐ Acetaminophen **1.2. Opioids** **1.2.1 IV Opioids** ☐ Morphine ☐ Hydromorphone (Dilaudid) ☐ Fentanyl (Sublimaze, Duragesic) ☐ Meperedine (Demerol) **1.2.2. Oral opioids** ☐ Hydrocodone (Vicodin, Lortab, Norco) ☐ Oxycodone (Roxicet, Percocet, Roxicodone) ☐ Fentanyl-transmucosal, sublingual (Actiq, Fentora, Onsolis) ☐ Methadone ☐ Tapentadol (Nucynta) ☐ Tilidine	**1.3. Adjuvant Medications with Sedative Properties** **1.3.1. Tricyclic antidepressants (TCAs)** ☐ Amitriptyline ☐ Nortriptyline (Pamelor) ☐ Desipramine (Norpramin) ☐ Amoxapine ☐ Impramine **1.3.2. Benzodiazepines** ☐ Triazolam (Halcion) ☐ Temazepam (Restoril) ☐ Lorazepam (Ativan) ☐ Diazepam (Valium) ☐ Clonazepam (Klonopin) ☐ Alprazolam (Xanax) **1.3.3. Sleep Aides** ☐ Zoldipem (Ambien) ☐ Ramelteon (Rozerem) ☐ Eszopiclone (Lunesta) ☐ _____ **1.3.3. Selective serotonin reuptake inhibitors** ☐ Escitalopram (Lexapro) ☐ Fluoxetine (Prozac, Sarafem, Symbyax) ☐ Paroxetine (Paxil, Paxil CR, Pexeva) ☐ Sertraline (Zoloft) ☐ Citalopram (Celexa)	**1.3.4. Anti- Convulsants** ☐ Pregabalin (Lyrica) ☐ Gabapentin (Neurontin, Gabarone) ☐ Carbamezapine (Carbatrol, Equetro, Tegretol) **1.3.5. Antiemetics** ☐ Diphenhydramine (Benadryl) ☐ Promethazine (Phenergan) ☐ Scopolamine (patch) ☐ Prochlorperazine (generic) ☐ Dimenhydrinate (Dramamine) **1.3.6. Muscle Relaxants** ☐ Cyclobenzaprine (Flexeril, Amrix) ☐ Metaxlone (Skelaxin) ☐ SOMA (Carisoprodol) ☐ Robaxin (Methocarbamol) ☐ Tizanidine (Zanaflex) ☐ Baclofen (Kemstro, Lioresal, and Gablofen)

Appendix D: American Society of Anesthesiologists Physical Status

The American Society of Anesthesiologists (ASA) physical status classification is a grading system for assessing the health of patients before surgery.

ASA PS Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient.	Healthy, non-smoking, no or minimal alcohol use.
ASA II	A patient with mild systemic disease.	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity ((30 < Body Mass Index (BMI) < 40)), well-controlled Diabetes Mellitus (DM)/ hypertension (HTN), mild lung disease.
ASA III	A patient with severe systemic disease.	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life.	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis.
ASA V	A moribund patient who is not expected to survive without the operation.	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction.
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes.	

*The addition of “E” denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part).

Appendix E: ARISCAT, POSPOM and NEWS scores calculation

ARISCAT risk score calculation[14]

High or intermediate risk for postoperative pulmonary complications following abdominal surgery: ARISCAT risk score ≥ 26

Risk for PPC of Variables Selected for the Logistic Regression Model			
	Multivariate Analysis	**β Coefficients**	**Risk Score§**
	OR (95% CI) N = 1624		
Age (yr)			
≤ 50	1		
51 – 80	1.4 (0.6 - 3.3)	0.331	**3**
> 80	5.1 (1.9 - 13.3)	1.619	**16**
Preoperative SpO_2, %			
≥ 96	1		
91 – 95	2.2 (1.2 - 4.2)	0.802	**8**
≤ 90	10.7 (4.1 - 28.1)	2.375	**24**
Respiratory infection in the last month	5.5 (2.6 - 11.5)	1.698	**17**
Preoperative anemia (≤ 10 g/dL)	3.0 (1.4 - 6.5)	1.105	**11**
Surgical incision			
Peripheral	1		
Upper abdominal	4.4 (2.3 - 8.5)	1.480	**15**
Intrathoracic	11.4 (4.9 - 26.0)	2.431	**24**
Duration of surgery, h			
≤ 2	1		
> 2 to 3	4.9 (2.4 - 10.1)	1.593	**16**
> 3	9.7 (4.7 - 19.9)	2.268	**23**
Emergency procedure	2.2 (1.04 - 4.5)	0.768	**8**

Abbreviations: CI, confidence interval; OR, odds ratio; SpO_2, oxyhemoglobin saturation by pulse oximetry breathing air in supine Position: PPC, postoperative pulmonary complications.

† The simplified risk score is the sum of each logistic regression coefficient multiplied by 10, after rounding off its value.

POSPOM risk score calculation[4]

POSPOM Score is an accurate risk score for predicting in-hospital mortality in patients undergoing surgery.

Age	Pointed assigned
18-20	+0
21-25	+1
26-30	+2
31-35	+3
36-40	+4
41-45	+5
46-50	+6
51-55	+7
56-60	+8
61-65	+9
66-70	+10
71-75	+11
76-80	+12
81-85	+13
86-90	+14
91-95	+15
>95	+16

Comorbidity	Points assigned
Ischemic heart disease	+1
Cardiac arrhythmia or heart blocks	+1
Chronic heart failure or cardiomyopathy	+4
Peripheral vascular disease	+1
Dementia	+2
Cerebrovascular disease	+1
Hemiplegia	+4
Chronic obstructive pulmonary disease	+1
Chronic respiratory failure	+3
Chronic alcohol abuse	+4
Cancer	+4
Diabetes	+1
Transplanted organ(s)	+2
Preoperative chronic hemodialysis	+1
Chronic renal failure	+2

Planned Surgery	Points assigned
Endoscopic digestive	+0
Ophthalmologic	+0
Gynecologic	+6
Other orthopedic	+6
Interventional cardiorhythmology	+8
Arthroplasty and spine	+9
Ear, nose and throat (ENT)	+9
Minor urologic	+9
Plastic	+9
Major urologic	+12
Others surgery	+12
Minor hepatic	+12
Minor gastrointestinal	+13
Renal transplant	+13
Minor vascular	+13
Orthopedic trauma	+14
Major hepatic	+15
Thoracic	+15
Neuro	+15
Major vascular	+16
Major gastrointestinal	+16
Interventional neuroradiology	+17
Cardiac	+17
Transplant	+22
Multiple trauma related	+22

TOTAL SCORE
POSPOM <20: Average risk (less than 0.4% predicted risk)
POSPOM=24: 3 times the average risk (1.2%)
POSPOM=28: 10 times the average risk (4.2%)
POSPOM=33: 40 times the average risk (16.5%)

Total Points	Predicted risk (%) of in-hospital mortality	Total Points	Predicted risk (%) of in-hospital mortality
0	<0.001	26	2.329
1	0.001	27	3.126
2	0.002	28	4.184
3	0.002	29	5.579
4	0.003	30	7.403
5	0.004	31	9.763
6	0.006	32	12.771
7	0.008	33	16.535
8	0.010	34	21.140
9	0.014	35	26.619
10	0.019	36	32.925
11	0.026	37	39.912
12	0.035	38	47.336
13	0.047	39	54.879
14	0.063	40	62.205
15	0.086	41	69.012
16	0.116	42	75.085
17	0.157	43	80.307
18	0.212	44	84.659
19	0.286	45	88.190
20	0.387	46	90.995
21	0.523	47	93.185
22	0.706	48	94.872
23	0.953	49	96.159
24	1.286	50	97.133
25	1.732	>51	>97.865

NEWS score calculation[24]

Criteria	Point Value
Respiratory Rate (breaths per minute)	
≤8	+3
9-11	+1
12-20	0
21-24	+2
≥25	+3
Oxygen Saturation (%)	
≤91	+3
92-93	+2
94-95	+1
≥96	0
Any Supplemental Oxygen	
Yes	+1
No	0
Temperature in °C (°F)	
≤35.0 (95)	+3
35.1-36.0 (95.1-96.8)	+1
36.1-38.0 (96.9-100.4)	0
38.1-39.0 (100.5-102.2)	+1
≥39.1 (≥102.3)	+2
Systolic BP	
≤90	+3
91-100	+2
101-110	+1
111-219	0
≥220	+3

Heart Rate (beats per minute)	
≤40	+3
41-50	+1
51-90	0
91-110	+1
111-130	+2
≥131	+3
AVPU (Alert, Voice, Pain, Unresponsive)	
A	0
V, P, or U	+3

- A low score (NEWS 1–4) should prompt assessment by a competent registered nurse who should decide if a change to frequency of clinical monitoring or an escalation of clinical care is required.
- A medium score (i.e. NEWS of 5–6 or a RED score) should prompt an urgent review by a clinician skilled with competencies in the assessment of acute illness – usually a ward-based doctor or acute team nurse, who should consider whether escalation of care to a team with critical-care skills is required (i.e. critical care outreach team).
  - A RED score refers to an extreme variation in a single physiological parameter (i.e., a score of 3 on the NEWS chart in any one physiological parameter, colored RED to aid identification; e.g., heart rate
- A high score (NEWS ≥7) should prompt emergency assessment by a clinical team/critical care outreach team with critical-care competencies and usually transfer of the patient to a higher dependency care area.

4. Version History

Version	Summary of Changes	Author(s)/Title
1.0, 24 Jan, 2018	Not Applicable, New Document	[redacted]
2.0, 19 Jun, 2019	**Title Page:** Updated address for Covidien Services Europe **Section 2:** Updated address for Covidien Services Europe. Updated expected total patient recruitment from 300 to 210; 70 to be recruited in Phase I and 140 in Phase II. Updated Inclusion criteria No. 1 to indicate that patients may be enrolled if the they have POSPOM score ≥ 24 OR ARISCAT score ≥ 26. **Section 5:** Updated expected total patient recruitment from 300 to 210; 70 to be recruited in Phase I and 140 in Phase II. Indicated that sites will have at least one month, as opposed to one week to familiarize themselves unblinded devices. Updated Figure 1 to reflect the above. **Section 7.3:** Updated Inclusion criteria No. 1 to indicate that patients may be enrolled if the they have POSPOM score ≥ 24 OR ARISCAT score ≥ 26. **Section 8.7:** Updated to indicate that the point of patient exit from the study will not be the end of the monitoring period, but instead upon discharge from the hospital. Clarified that AEs are reportable during this period. **Section 8.8**: Updated to indicate that Date of patient discharge from hospital should be collected at study exit. **Section 12.1:** Updated total patient population from 300 to 210.	[redacted]