Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	**PRODIGY** PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY
Clinical Investigation Plan Identifier	COVMOPO0560
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Sponsor/Local Sponsor	**Global and US** Covidien LP Medtronic Minimally Invasive Therapy Group, Patient Monitoring and Recovery 6135 Gunbarrel Avenue, Boulder, Colorado, 80301 USA **Europe** Covidien LP Represented by: Covidien Services Europe Ltd* 1st Floor Block G Cherrywood Science & Technology Park, Loughlinstown, Dublin 18 Ireland **Japan** Covidien Japan Inc. 2-70 Konan 1-chome Minato-ku, Tokyo, Japan 108-0075 **Singapore** Covidien Private Limited Mapletree Business City 50 Pasir Panjang Road, #04-51 Singapore 117384

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Initial version	Nicoletta Grovale, RCC Clinical Research Manager
2.0	• Sponsor address update, list of approvers deleted, typos corrected	Nicoletta Grovale, RCC Clinical Research Manager

3.0	• Addition of Japan and Singapore geographies and requirements incorporated. • Removed secondary objectives 2, 3, 4, and 6 and updated secondary endpoints accordingly as they were not required. Updated secondary objective for evaluating IPI to also look at capnography parameters of $etCO_2$, SpO_2, and RR. • Respiratory depression definition for the primary endpoint updated to include consideration of both monitoring and clinical data. • Respiratory episode criteria updated to be consistent with Capnostream manual alarms. • Added additional methods for minimizing potential bias. • Added rationale section per CIP standard template requirement. • Updated product description to include additional Capnostream model and accessories. • Removed description of WiFi converter, laptop and tablets from product description as the data collection method for device memory data updated to use of memory stick. • Added manufacturer information. • Added intended population statement. • Added equipment, product use, product storage, product return and product accountability section. • Updated product training requirement with training and device transfer testing requirement. • Inclusion criteria updated with use of parenteral opioids, and removal of separate listing of routes and timing. Age requirements for adult definition added for Japan and Singapore. • Exclusion criteria updated with additional of length of hospital stay, refinement of life expectancy for all subjects. Removed BMI exclusion, and alcohol or drug history. Replaced criteria indicating vulnerable populations with vulnerable population exclusion as defined by ISO. • Data collection requirements updated with screening and requirement of study exit for all subjects. • Capnography monitoring period added the removal of the alarm feature, blinding the monitor screen and removing documentation of interventions on the tablet. Actions/interventions will be documented on the adverse event form with source from the medical record. • Removed study preparation procedures as these are required and documented prior to the CIP and not part of the study conduct procedures. • Updated adverse event section with required data collection.	Christine Greening, PRODIGY Global Program Manager

	• Removed study contact names as this information is provided under separate cover for the sites. • Clinical Endpoint Committee changed to Clinical Event Committee as this aligns with standard terminology. • Added RD event monitoring and sample size re-estimation plan. • Removed interim analysis for secondary objectives as it no longer applies with the deletion of those secondary objectives. • Data management section updated with the flash memory drive for Capnostream device memory data transfer. • Removed reporting tables as this information is included within the relevant sections. • Added appendix of study relevant medications. • Grammatical, formatting and typographical corrections incorporated.	

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2. Glossary

Term	Abbreviation	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.
Adverse Device Effect	ADE	Adverse event related to the use of an investigational medical device.
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.
Capnography	CO_2 monitoring	A non-invasive method for monitoring the level of carbon dioxide in exhaled breath ($etCO_2$).
Clinical Investigation Plan	CIP	The present document describing PRODIGY Study Protocol.
Clinical Event Committee	CEC	An independent committee of experts not participating in the clinical study that provides adjudication of study specific endpoints and/or events utilizing study-specific or consensus definitions available in the field.
Electronic Case Report Forms	eCRF	Forms where the clinical data are collected. eCRF is the electronic version of case report forms.
Ethical Committee / Institutional Review Board	EC / IRB	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 subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects.
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.
Emergency Room	ER	Medical treatment facility specializing in emergency medicine, the acute care of patients who present

Term	Abbreviation	Definition
		without prior appointment; either by their own means or by that of an ambulance.
Fractional inspired carbon dioxide	$FiCO_2$	The numeric partial pressure of carbon dioxide present during inhalation.
Intensive Care Unit	ICU	Acute care with 24 hour coverage. Patients may be directly transferred direct 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.
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 oxygemoglobin in arterial blood as it leaves the heart.
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.
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 clinical diagnosis made after reviewing monitoring data in conjunction with the clinical data and consistent with accepted pathophysiologic mechanisms.
Respiratory Opioid-Related Adverse Events (ORADE)	rORADE	An episode of respiratory compromise that is related to opioid analgesia therapy.
Respiration Rate	RR	The count of breaths per minute based upon the carbon dioxide cycle as measured by capnography.

Term	Abbreviation	Definition
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, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect.
Standard Operating Procedures	SOP	Medtronic Quality Standard Operating Procedures
Vulnerable subject		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. EXAMPLE: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects 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.

3. Synopsis

Title	PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY)
Clinical Study Type	Post-market interventional study
Product Name	Capnostream™ monitor and its accessories, including any sensor for SpO_2 measurements and filter line for $etCO_2$ sampling.
Sponsor / Local Sponsor	Global and US Sponsor Covidien LP* Medtronic Minimally Invasive Therapy Group, Patient Monitoring and Recovery 6135 Gunbarrel Avenue, Boulder, Colorado 80301 USA Europe Covidien LP Represented by: Covidien Services Europe Ltd* 1st Floor Block G Cherrywood Science & Technology Park, Loughlinstown, Dublin 18 Ireland Japan Covidien Japan Inc. 2-70 Konan 1-chome Minato-ku, Tokyo, Japan 108-0075 Singapore Covidien Private Limited Mapletree Business City 50 Pasir Panjang Road, #04-51 Singapore 117384 **Covidien LP and Covidien Services Europe Ltd are indirect wholly owned subsidiaries of Medtronic plc.*
Investigation Purpose	The purpose of this study is to derive and validate a risk assessment tool derived from continuous respiratory monitoring and clinical data that can identify patients at greater risk of respiratory depression (RD) episodes when receiving parenteral opioid therapy on the hospital ward. The developed RD risk assessment tool may be used as a guide in identifying patients at risk of RD who could benefit from capnographic monitoring.
Product Status	Products used are those commercially available (cleared by FDA, MHLW/PMDA and CE-Marked) and used within intended use in the participating geographies.

Primary Objective	The primary objective of this study is to derive and validate a risk assessment tool to identify subjects at risk of having RD while undergoing parenteral opioid therapy on the hospital ward.
Secondary Objective(s)	Secondary objectives are: 1. To compare subjects that will develop RD versus subjects that will not develop RD (in terms of parameters additional to those needed for primary objective, see Section 5.4 for details). 2. To characterize the predictive values of etCO2, RR, SpO2, and the IPI in predicting RD and ORADE. 3. To measure health care utilization costs during the study period.
Study Design	PRODIGY is a prospective, multi-center, post-market interventional, international cohort study. The study population consists of subjects of adult age (≥18 in US and Europe, ≥20 in Japan, ≥21 in Singapore) receiving parenteral opioid therapy for pain while on the hospital ward. A derivation cohort will be used to derive the risk assessment tool. An internal validation cohort will be used for evaluating the prognostic value of the score for the prediction of RD. Capnography and pulse oximetry monitoring device data will be collected as well as clinical events related to respiratory depression. Subjects will be monitored per standard of care.
Sample Size	Approximately 1650 patients will be enrolled in up to 16 centers from United States (US), Europe and Asia. Geographic distribution of sites is anticipated as 8 sites (50%) in the US, 5 (30%) in Europe and 3 (20%) in Asia. Additional centers could be added during the course of the study if enrollment rate is lower than expected. Each participating center may involve in the study one or more wards, based on its distribution of patients receiving opioid therapy. Each participating site is expected to enroll at least 20 subjects per month. Enrollment at any single site will be limited to 20% (approximately 330 subjects) to ensure poolability of the data across sites and reduce potential bias. The study is expected to last around 10-13 months (10-12 months of enrollment plus 30 days from the last enrolled subject). Each subject will be followed in the study for approximately 30 days.
Inclusion/Exclusion Criteria	The following criteria must be met for subjects to be eligible for inclusion in the study: 1. Patients receiving parenteral opioid therapy (for post-surgical or non-surgical) pain on the hospital ward.

	2. Adult age (≥18 year old in US and Europe; ≥20 years old in Japan; ≥21 years old in Singapore). 3. Patient is able and willing to give informed consent. The following criteria are exclusions for study participation: 1. Expected length of stay ≤ 24 hours. 2. Patient is receiving intrathecal opioids. 3. Post-surgical patients with American Society of Anesthesiologists physical status (ASA PS) V or higher. 4. Patients with the status of Do Not Resucitate (DNR), hospice, or receiving end of life therapy. 5. Ventilated or intubated patients. 6. Patient is unwilling or unable to comply fully with study procedures (including non-toleration of the capnography cannula) due to any disease condition which can raise doubt about compliance and influencing the study outcome. 7. Patient is a member of a vulnerable population, including legal incapacity or evidence that a subject cannot understand the purpose and risks of the study, regardless of authorized representative support. 8. Patient is participating in another potentially confounding drug or device clinical study.
Study Procedures and Assessments	Screening will be completed to identify potential subjects who will be admitted on the wards. If the patient is potentially eligible and willing to consider participation, written informed consent must be obtained. A review of subject files by the investigator is required to determine preliminary eligibility according to subject inclusion and exclusion criteria. Subjects are considered a screen failure if inclusion / exclusion criteria are not met prior to monitoring on the hospital ward. Each subject will be clinically monitored through standard methods (as per clinical practice of the site). Additional continuous data from the Capnostream monitor will be collected for a maximum of 48 hours to identify potential indictors of respiratory depression. The alarm feature of the monitoring device will be silenced and the screen information blinded. A periodic check during the monitoring period should be completed to ensure the etCO2 filter line and SpO2 sensor are appropriately fitted on the subject. Monitoring of capnography and pulse oximeter data with the Capnostream monitor will start after opioid therapy has been initiated for subjects that will receive their first opioid therapy dose while on the hospital ward. The monitoring period will start for subjects once they arrive on the ward, for those subjects where opioid therapy was initiated prior to arrival on the hospital ward.

	Monitoring may be discontinued after a minimum of 4 hours from the last dose of opioid therapy received or if the subject is discharged from the hospital ward. Occurrence of any respiratory adverse events (AE), serious adverse events, or device deficiencies will be documented. AE relatedness to opioid therapy or the device will also be identified. At the end of the data collection period the subject will be treated according to the hospital clinical practice and remain in the study for a maximum period of 30 days from the start of opioid therapy. A 1 month follow up (performed by phone if patient has been discharged) will be performed to collect information on healthcare resource utilization (hospital length of stay, hospital readmission and related primary diagnosis), and serious adverse events resulting in death or respiratory ORADE occurrence.
Statistics	The size of the study cohort has been calculated to provide independent samples for derivation and validation cohort. At the study closure, subjects will be randomly assigned (2:1) into two groups to create a derivation cohort with 2/3 of the subjects and an internal validation cohort with the other 1/3 allowing the following calculation. The size of the derivation cohort has been calculated to provide at least 10 events per variable that we expect to enter into the logistic regression model. Recording at least 120 RD events would allow around 12 predictor variables to be entered into logistic regression. Assuming an incidence of 12% of subjects with RD episodes and 12-variables for prediction rule, a sample size of 1000 subjects is needed for the derivation cohort. Since the derivation cohort will be 2/3 of the total sample size, the internal validation cohort will be 1/3 (500 subjects) of the total sample size. Considering a 10% attrition of (ie withdrawals/dropouts/screening failure), the total sample size needed is 1650 subjects.

4. Introduction

4.1. Background

Opioid analgesia is the primary pharmacologic intervention for managing pain in hospitalized patients[1]. Opioid therapy is indeed the gold standard for treatment of post-surgical pain in hospital ward but also the majority of non-surgical patients admitted in hospital are exposed to opioids[2]. They can be administered orally, by Patient Controlled Analgesia (PCA), by epidural or intrathecal infusions, by intravenous or intramuscular analgesia. In recent years there have been increasing concerns over unmonitored mortality and morbidity in patients during opioid therapy for acute pain[3]. Up to 80% of patients who received opioid analgesics experience Opioid-Related Adverse Drug Events (ORADEs)[4]. In post-surgical patients, ORADEs have been shown to significantly increase patient's hospital length of stay and related costs[4]. Improper patient monitoring has been reported by the Joint Commission as one of the main causes of ORADEs[1,5].

One of the major opioid side effects includes respiratory depression (RD), which causes alveolar hypoventilation and hypoxemia. The reported incidence of RD in post-surgical patients varied from 0.3% to 3.4% when only considering intervention rate (i.e. naxolone infusion)[3,6,7], while it is reported up to 21% and 41% when including also prolonged oxygen desaturation and bradypnea episodes, respectively[6,8]. If detected early, most cases of opioid-related RD can be treated with naloxone; however, severe cases can be fatal[9].

Respiratory compromise 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[10]. Detection of a patient's respiratory compromise status before progression can help avert unwarranted outcomes and the possible need for critical care. Despite this, there are no universally accepted guidelines to direct effective and safe assessment and monitoring practices for patients receiving in-hospital opioid analgesia[1]. Current standard of care for respiratory monitoring of hospital ward patients receiving opioid therapy is intermittent documentation of oxygen saturation (SpO_2) value (e.g. performed at 4 to 6 hours intervals)[6,8]. Some centers perform continuous SpO_2 monitoring to patients considered at risk to develop RD, but the decision is usually left to physician discretion. Respiratory rate (RR) is often determined by clinician assessment though manual respiration counts[9]. Typically, only some high-risk patients are monitored by capnography, a technology that assesses real-time ventilation by continuous measuring of SpO_2, RR and the concentration of exhaled end tidal carbon dioxide ($etCO_2$).

Pulse oximetry alone can lead to inaccurate assessment of patients' condition, especially when supplemental oxygen is needed: the Anesthesia Patient Safety Foundation recommended the use of continuous electronic monitoring of oxygenation and ventilation for all patients undergoing opioid therapy in the postoperative period and capnography monitoring when supplemental oxygen is needed[11]. Even at low respiratory rate, SpO_2 could be maintained for a certain period, thus delaying the RD detection. Many patients who breathe inadequately at rest or during sleep may present normal or near-normal oxygen saturation after they are awakened[8].

Growing evidence supports the use of capnography for earlier and more reliable warnings of RD in postoperative patients in the general ward, compared with pulse oximetry[12–15]. It has been demonstrated that RD detected by capnography is significantly higher than RD detected by oxygen desaturation alone

in post-surgical patients using PCA[6], while there are no data in literature related to capnography monitoring in non-surgical patients.

Main risk factors for developing RD have been widely studied in literature, particularly for post-surgical patients. Most reported include: sleep apnea, obesity, snoring, old age, post-surgery, increased opioid dose requirement, concomitant use of other sedating medications, comorbidities like preexisting pulmonary or cardiac disease, PCA use and smoking[1,4,7,16,17].

The need of a simple tool to stratify patients at risk to develop RD has been underlined by several authors[1,7,16,17]. Such a tool will also help health care providers in selecting the best candidate for capnographic monitoring. Previous attempts to develop prediction scores failed to show a significant sensitivity, probably due to limited sample size and retrospective design[17] or were only limited to surgical patients[7].

4.2. Purpose

The purpose of this study is to derive and validate a risk assessment tool derived from continuous respiratory monitoring and clinical data that can identify patients at greater risk of respiratory depression (RD) episodes when receiving parenteral opioid therapy on the hospital ward. The developed RD risk assessment tool may be used as a guide in identifying patients at risk of RD who could benefit from capnographic monitoring.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The primary objective of this study is to derive and validate a risk assessment tool to identify subjects at risk of having RD while undergoing opioid therapy on the hospital ward.

5.1.2. Secondary Objective(s)

The study secondary objectives are as follows:

1. To compare subjects that will develop RD versus subjects that will not develop RD (in terms of parameters additional to those needed for primary objective, see Section 5.2.2 for details).
2. To characterize the predictive values of $etCO_2$, RR, SpO_2 and the IPI in predicting RD and ORADE.
3. To measure health care utilization costs during the study period.

5.2. Endpoints

5.2.1. Primary Endpoint

Respiratory depression is a clinical diagnosis made after reviewing monitoring data in conjunction with the clinical data and consistent with accepted pathophysiologic mechanisms.

The primary endpoint used to derive the score will be the incidence of RD episodes captured by continuous capnography and pulse oximetry measurements recorded on the Capnostream device memory data in conjunction with the clinical data as reported by the investigator.

RD determination will be validated by an independent Clinical Event Committee (CEC). The CEC will use both clinical data and monitor parameters specificed below as a guideline; if determination of an RD episode is clinically appropriate but outside of the guidelines a rationale will be provided.

Data suggestive of an RD episodes include any of the following:

- $etCO_2 \leq 15$ or ≥ 60 mmHg for ≥ 3 minutes.

or

- RR ≤ 5 breaths for ≥ 3 minutes.

or

- $SpO_2 \leq 85\%$ for ≥ 3 minutes.

or

- Apnea episode lasting > 30 seconds.

or

- Any respiratory Opioid-Related Adverse Event (rORADE).

5.2.2. Secondary Endpoint(s)

1. RD risk subjects versus no-risk subjects will be compared in terms of:
    - Incidence of AE's and actions taken.
    - Healthcare resource utilization (including hospital length of stay, 30 days readmission rate and primary diagnosis upon readmission).
    - Subject mortality at 30 days.
2. The predictive value (sensitivity, specificity, etc.) of etCO2, RR, SpO2, and IPI will be correlated with the occurrence of RD and ORADE.
3. Cost associated with events and actions taken will be estimated retrospectively using standard cost data from different countries.

6. Study Design

PRODIGY is a prospective, post-market interventional, multi-center, international cohort study.

A derivation cohort will be used to derive the risk assessment tool. An internal validation cohort will be used for evaluating the prognostic value of the score for the prediction of RD. Capnography and pulse oximetry monitoring device data will be collected as well as clinical data related to respiratory depression. Subjects will be monitored per standard of care. Enrollment at any single site will be limited to 20% (approximately 330 subjects) 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 subjects via screening
- Both surgical and non-surgical candidates are eligible as event rates may vary
- Adjudication of RD events by an independent review committee
- Diverse geographical site representation to account for difference in practice

- Standard procedures and data collection requirements with a common electronic database for all sites
- Provision of product for all study subjects

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

Approximately 1650 subjects will be enrolled in up to 16 centers from the United States (US), Europe and Asia. Geographic distribution of sites is anticipated as 8 sites (50%) in the US, 5 (30%) in Europe and 3 (20%) in Asia. Additional locations may be added during the course of the study.

6.1. Duration

At least 20 subjects per month are expected to be enrolled at each participating center. Each participating site may involve one or more wards, based on its distribution of subjects receiving opioid therapy.

The study is expected to last approximately 10-13 (10-12 months of enrollment plus 30 days from the last enrolled subject). Not all the participating centers will be active at the moment of enrollment start.

Each subject will be followed-up for a maximum period of 30 days.

6.2. Rationale

The need of a simple tool to stratify patients at risk for developing RD has been identified to understand individuals that may benefit from capnographic monitoring. The chosen study design was based on predictive models that are often used to predict the probability that a subject with a given set of risk factors will experience an outcome. However the predictive ability of the model should be evaluated before any use in clinical practice. This is known as the validation step. The standard regression method used for analysis could accurately predict outcomes for subjects in the dataset used to develop the model, but may often perform less well in a new subject group. This difference is due to the random variation present in the development dataset. Therefore, the need to validate the risk score in another validating set of subjects has been incorporated.

This study will also collect data on a high number of subjects monitored by capnographic monitoring, thus allowing understanding of the real incidence of RD, especially in non-surgical subjects for which there are no data in the literature.

7. Product Description

7.1. General

The Capnostream monitoring system includes a capnograph/pulse oximeter monitor, sampling line for end tidal carbon dioxide ($etCO_2$), and pulse oximetry sensor for measuring the peripheral oxygen saturation of arterial hemoglobin (SpO_2).

All devices used in this study are commercially available (cleared by FDA, MHLW/PMDA and CE-Marked) and used within intended use in the participating geographies. The Instruction for Use (IFU) manual is provided with the product in the local language.

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

Table 1. Medtronic Market-Released Devices and Accessory Components

Model or Version	Product
CS08651-02 PM35MN	Capnostream Monitor • Capnostream™ 20p Portable Bedside Monitor Capnograph/Pulse Oximeter • Capnostream™ 35 Portable Respiratory Monitor
Version 7.5 (Japan only) Version 8.5	Capnostream Software
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
OxiMax Max-A OxiMax Max-AL OxiMax MaxN MaxFast SoftCare	Nellcor™ SpO_2 Sensor
	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

7.1.1. 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.
- Fractional inspired carbon dioxide ($FiCO_2$) - level of carbon dioxide present during inhalation.
- 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 1. Capnostream 20$_p$

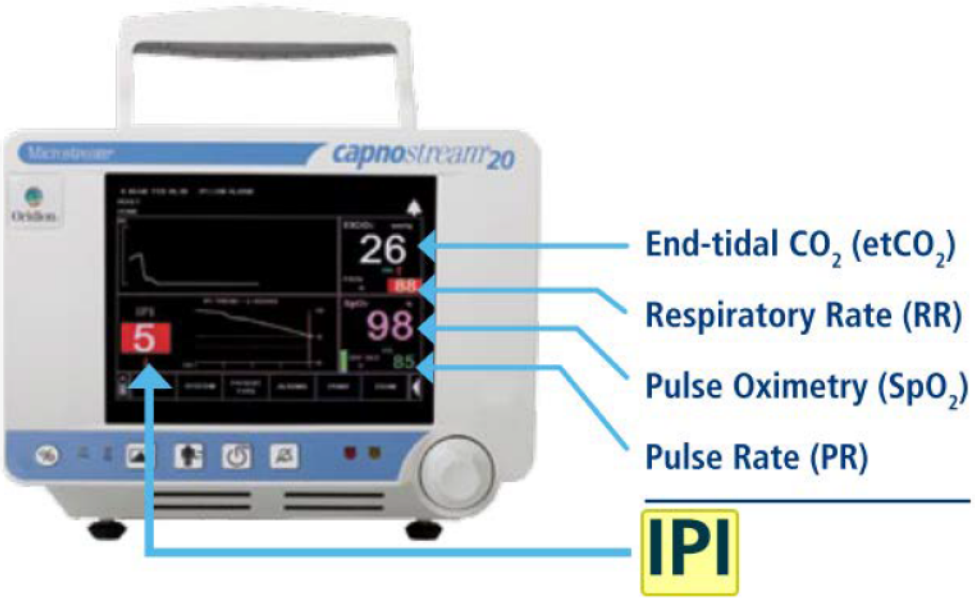


Figure 2. Capnostream 35

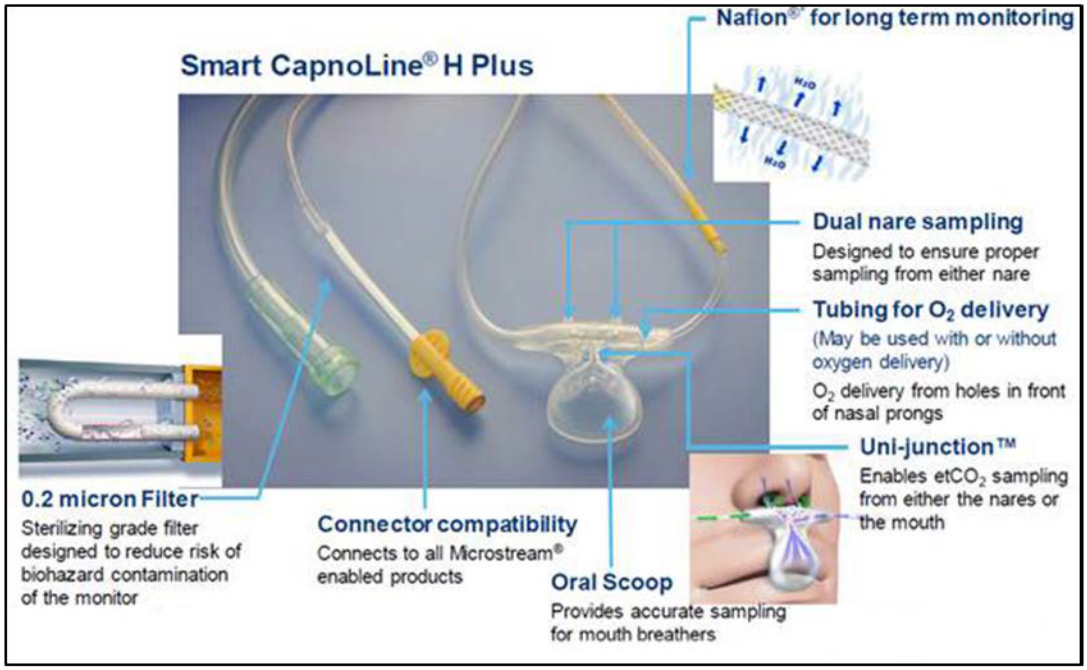
7.1.2. End-tidal Carbon Dioxide ($etCO_2$) Sampling Line

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) are a disposable single use sampling line.

Each study subject 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 would be delivered per usual clinical practice. The supplemental oxygen is not provided through the monitor.

Figure 3. $etCO_2$ Sampling Line



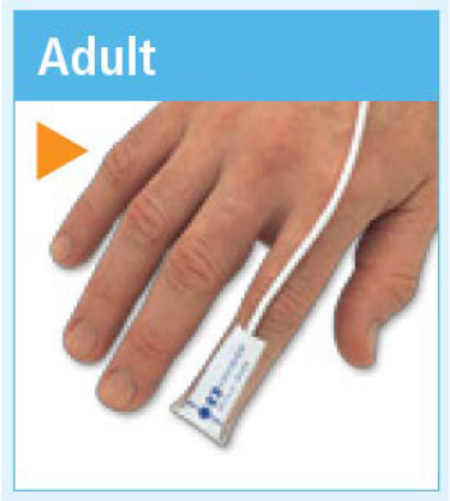
7.1.3. Peripheral Oxygen Saturation (SpO_2) Sensor

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 cyle determine the SpO_2.

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

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

Figure 4. SpO_2 Sensor



7.2. Intended Population

Intended Use

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 (SpO_2) 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 Capnostream™ 35 is a portable capnograph/pulse oximeter, intended to provide professionally trained health care providers with continuous non-invasive monitoring of carbon dioxide concentration of the expired and inspired breath, respiration rate, arterial oxygen saturation (SpO2) and pulse rate of adult, pediatric , and neonatal patients. The pulse oximeter is intended for use during both no motion and motion conditions and for patients who are well or poorly perfused. The device is intended for use in hospitals, hospital-type facilities, during intra-hospital transport, and out-of-hospital Emergency Medical Service applications that include ground and air transport.

7.3. Equipment

Calibration information is provided in the Capnostream manual. Any additional maintenance or cleaning procedures should follow the operator's institution guidelines.

7.4. Product Use

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

7.5. Product Training Requirements

Product information will be included in the study training materials. The device data transfer process will be tested and verified during the site initiation process. In addition, device data from the first ten subjects at each site will be collected and transferred through the device data transfer process as soon as

possible. This will be completed to ensure data quality and identify any process improvements to maximize quality, as needed.

7.6. Product Receipt and Tracking

Participating sites will be provided with a sufficient number of Capnostream monitors, if not already present. In addition, a sufficient number of $etCO_2$ sample lines and SpO_2 Sensors will be provided.

The following records will be maintained at minimum for product delivery, receipt and tracking at the site: dates, quantities received, lot/serial numbers, and expiration dates, as applicable.

7.7. Product Storage

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

7.8. Product Return

Product provided to the site shall be returned at the end of the study. (Excludes consumable product 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.

7.9. Product Accountability

Reconciliation of product received, used and returned will be completed at the end of the study.

8. Selection of Subjects

8.1. Study Population

The target population consists of subjects of adult age (≥18 in US and Europe, ≥20 in Japan, ≥21 in Singapore) receiving parenteral opioid therapy on the hospital ward for (post-surgical or non-surgical) pain.

8.2. Subject Enrollment

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

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

8.3. Inclusion Criteria

1. Patients receiving parenteral opioid therapy (for post-surgical or non-surgical) pain on the hospital ward.
2. Adult age (≥18 year old; ≥20 years old in Japan; ≥21 years old in Singapore).
3. Patient is able and willing to give informed consent.

8.4. Exclusion Criteria

1. Expected length of stay ≤24 hours.
2. Patient is receiving intrathecal opioids.
3. Post-surgical patients with American Society of Anesthesiologists physical status (ASA PS) V or higher.
4. Patients with the status of Do Not Resuscitate (DNR), hospice, or receiving end of life therapy.
5. Ventilated or intubated patients.
6. Patient is unwilling or unable to comply fully with study procedures (including non-toleration of the capnography cannula) due to any disease condition which can raise doubt about compliance and influencing the study outcome.
7. Patient is a member of a vulnerable population, includinglegal incapacity or evidence that a subject cannot understand the purpose and risks of the study, regardless of authorized representative support.
8. Patient is participating in another potentially confounding drug or device clinical study.

9. Study Procedures

9.1. Schedule of Events

Data will be collected for Screening, Enrollment Visit, the Capnographic Monitoring Period, 1 month Follow Up Visit, and Study Exit. 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 subject exits the study.

Table 2. Data Collection Requirements

Data	Screening Evaluation	Enrollment	Capnography Monitoring	1 Month Follow up	Study Exit
Informed Consent	X				
Inclusion/Exclusion Criteria Evaluation	X				
Medical History		X			
Demographic & Physical Exam		X			
Vital Signs		X	X		
Supplemental Oxygen Use		X	X		
Surgery Information		X			
Care Pathway			X		
Monitoring Duration			X		
Medications		X	X		
Adverse Events		X	X	X	X
Device Memory Data			X		
Product Information			X		
Device Deficiencies			X		
Protocol Deviations	X	X	X	X	X
Healthcare Resource Utilization				X	X

9.2. Subject Screening

A consideration of all potential subjects is recommended to minimize selection bias. Track potential subjects on the Screening eCRF.

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

- Informed consent signature date
- Inclusion / exclusion criterial evaluation

Subjects will be considered a screen failure and immediately exited from the study if the subject 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 Evaluation eCRF. Document the exit by completing the Study Exit eCRF.

9.3. Subject 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 administration of opioid medication. In addition, written informed consent must be obtained pre-operatively, if surgery is applicable.

Well in advance of the consent discussion, the subject should receive the EC/IRB 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 subject, and that informed consent was freely given.

After all persons have signed and dated the Informed Consent Form, the investigator must provide the subject 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 subject 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 subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the EC/IRB. After approval by the EC/IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

9.4. Prior and Concomitant Medications

Opioids, medications with sedative properties and concomitant pain medications will be documented on the Medication eCRF. In addition, administration of a reversal agent should be documented on the Medication eCRF.

Medications will be collected at study enrollment and during the monitoring period. In addition, for subjects who had surgery, medications relevant to the study used during surgery and recovery will be documented.

See appendice 2 for a list of potential medications.

9.5. Enrollment

The point of enrollment is informed consent completed and inclusion/exclusion criteria are confirmed per the screening evaluation.

Data collected for enrolled subjects includes:

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

9.6. Capnography Monitoring Period

Each subject will be clinically monitored through standard methods (as per clinical practice of the site). Additional continuous data from the Capnostream monitor will be collected for a maximum of 48 hours to identify potential indicators of respiratory depression.

Monitoring of capnography and pulse oximeter data with the Capnostream monitor will start after opioid therapy has been initiated for subjects that will receive their first opioid therapy dose while on the hospital ward. The monitoring period will start for subjects once they arrive on the ward, for those subjects where opioid therapy was initiated prior to arrival on the hospital ward.

Monitoring may be discontinued after a minimum of 4 hours from the last dose of opioid therapy received or if the subject is discharged from the hospital ward.

Monitoring duration may be determined in periods, as deemed clinically appropriate during opioid therapy. An example of monitoring split into three periods:

- Period 1: first 24 hours continuous monitoring after enrollment (mandatory).
- Period 2: 12 hours continuous monitoring (to be performed for guidance during the first night following Period 1, from 7pm to 7 am).
- Period 3: 12 hours continuous monitoring (to be performed for guidance during the second night following Period 1, from 7pm to 7 am).

The suggested monitoring setting for Periods 2 and 3 has been proposed to facilitate subject's motion during daytime, thus covering the nighttime period at higher risk of developing RD events[6]. The alarm feature of the monitoring device will be silenced and the screen information blinded. A periodic check during the monitoring period should be completed to ensure the $etCO_2$ filter line and SpO_2 sensor are appropriately fitted on the subject.

Apart from the capnographic monitoring, no other device or concomitant medications different from clinical practice may be used during PRODIGY Study.

The Monitoring eCRF will be completed to document:

- Care pathway (location/transfers within the hospital)
- Monitoring duration
- Vital signs
- Supplemental oxygen use
- Medications
- Product information

At the end of the monitoring period the subject will be treated according to the hospital clinical practice and remain in the study for a maximum period of 30 days from the start of opioid therapy.

9.7. 1-Month Follow Up

A 1 Month Follow Up visit (performed by phone if subject has been discharged) will be performed at 30 days (±10 days) from enrollment.

Complete the 1 Month Follow Up eCRF. In addition, complete the applicable eCRFs to collect information related to:

- Adverse Events, if applicable to understand if any occurrence such as ORADE occurrence or mortality.
- Healthcare resource utilization (including hospital length of stay, readmission rate and related primary diagnosis).

9.8. Study Exit

The Study Exit eCRF will be used to document that the subject has exited from the study. The reason for study exit will be captured on the Study Exit eCRF.

In addition, if the visit does not follow the 1-Month Follow-Up Visit, complete the applicable eCRFs to collect information related to:

- Adverse Events, if applicable to understand if any occurrence such as ORADE occurrence or mortality.
- Healthcare resource utilization (including hospital length of stay, readmission rate and related primary diagnosis).

If the study exit was for any reason other than normal study completion, see section 9.12 for information related to subject withdrawal or discontinuation.

9.9. Assessment of Safety

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

9.10. Recording Data

The investigator will clearly mark the clinical records to indicate that the subject is enrolled in this clinical study. Subject's medical record will be used as source documents. Worksheets could serve as source documentation in particular cases if a data field is not in the subject's medical record.

Capnostream device memory data will be the source for the number and duration of RD episodes. RD data reports will be derived from the device memory data. The reports are used for primary endpoint validation from the Clinical Event Committee.

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 subject 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. 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 investigation site team with a statement that it is a true reproduction of the original source document.

9.11. 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 subject 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/IRB 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 subject's interest. Such deviations from the Clinical Investigation Plan do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC/IRB, if applicable. Medtronic will inform the regulatory authorities, if required.

Any deviation which may occur multiple times over the course of the study on the same subject because of a permanent change in the subject's condition is only reportable once for each subject.

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.

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.).

9.12. Subject Withdrawal or Discontinuation

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

Possible reasons for withdrawn from the study are:

- Adverse Event;
- Subject is lost to follow-up;
- Subject withdrew consent;
- Investigator withdrew subject from the study for medical reasons;
- Investigator withdrew subject from the study due to inclusion/exclusion criteria not met (including opiod therapy not started).

If discontinuation is because of safety or lack of effectiveness, the subject shall be asked to be followed for collecting safety data outside the clinical study. A missed 1 Month Follow Up will be considered a Protocol Deviation and the reason should be documented on the Protocol Deviation eCRF.

Subjects will be considered lost-to-follow-up after three documented attempts of contact. The relative information will be documented in the medical record. In addition, complete a Study Exit eCRF.

Subjects withdrawn for reasons other than screen failure will not be replaced.

10. Risks and Benefits

10.1. Potential Risks

Devices used in this clinical study are commercially available Medtronic is not aware of any significant problems with this product. 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 subject's doctor prior to, during, and after the monitoring phase.

In addition, a part from the capnographic monitoring, subjects 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 capnographic monitoring are:

- 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. Subjects with known skin contact allergies to medical grade adhesives will not be recruited.
- 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.

10.2. Potential Benefits

Subjects' 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 subjects may benefit from the structured, well-controlled clinical surveillance provided during the first days of opioid therapy.

The information gained from this study could result in the improved management of subjects undergoing in-hospital opioid therapy. 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.

10.3. 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.
- Standard of care will be followed by the sites for the administration of opioid therapy. Additional surveillance will be provided for close monitoring and recording of the subjects clinical status.

11. Adverse Event Assessments

In this study the following Adverse Events (AE) will be collected:

- All AEs with an underlying respiratory cause
- All adverse device effects (ADE)
- All Serious Adverse Events (SAE) (including sepsis events or related to opioid therapy)

RD episodes will not be considered Adverse Events if the subject is asymptomatic and no actions are taken.

11.1. Definitions/Classifications

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

Where the definition indicates "device", it refers to <u>any</u> product used in the study. See product description section 7 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.
Serious Adverse Event	SAE	An adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) 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.

Term	Abbreviation	ISO Definition
		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.

11.2. 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.

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 global 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/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC/IRB	Submit to EC/IRB 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/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC/IRB	Submit to EC/IRB 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/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC/IRB	Submit to EC/IRB 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/IRB	Submit to EC/IRB 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/IRB	As per local reporting requirement.
Sponsor submit to:	

Regulatory Authorities	As per local reporting requirement.
EC/IRB	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/IRB	As per local reporting requirement.

12. Data Review Committees

This study will have the following Committees: Clinical Event Committee and Steering Committee.

No Data Monitoring Committee will be installed for this study as no interventions intended to prolong life or reduce risk of a major adverse health outcome are evaluated, for which favorable or unfavorable study results suggest study termination. Nor are there safety concerns suggesting the need for a Data Monitoring Committee.

12.1. Clinical Event Committee

The Clinical Event Committeee (CEC) is an independent committee of experts not participating in the clinical study that provides adjudication of study specific endpoints and/or events utilizing study-specific or consensus definitions available in the field. The committee will consist of a minimum of three (3) non-Medtronic experts experienced in evaluating respiratory compromise, respiratory depression, and interpreting continuous monitor data.

The CEC roles are to:

- Review AE's to classify the event as respiratory or non-respiratory.
- Review AE's to determine the relatedness (including device or opioid therapy).
- Review Respiratory Depression (RD) episodes and classify them as such based on the primary endpoint definition of RD.

Composition, roles and responsibilities of CEC will be described in a separate charter.

12.2. Steering Committee

The Steering Committee is composed of physicians with expertise in the area of Anesthesiology and capnographic monitoring, who will assume a leadership role in the overall study.

The Steering Committee's roles are to:

- Develop the protocol along with the sponsor, to ensure its scientific and statistical soundness;
- Review the conduct of the study;
- Help identify and resolve problems with recruitment or performance.

Composition, roles and responsibilities of Steering Committee will be described in a separate charter.

13. Statistical Design and Methods

13.1. Sample Size

The size of the study cohort has been calculated to provide independent samples for derivation and validation cohort. At the study closure, subjects will be randomly assigned (2:1) into two groups to create a derivation cohort with 2/3 of the subjects and an internal validation cohort with the other 1/3 allowing to the following calculation.

According to a generally accepted rule of thumb, at least 10 events per variable are expected to be entered into the logistic regression model[20]. The three following endpoints from RD definition have been taken into consideration to calculate the sample size (since we assumed that the variations in respect to enrollment values could be mostly included into these):

A. RR ≤ 8 bpm for ≥ 3 minutes
B. SpO_2 ≤ 85% for ≥ 3 minutes
C. $etCO_2$ ≥ 60 mmHg for ≥ 3 minutes

From literature the incidence of the above events is at minimum:

A = 1.4%[21].

B = 10%[8] (extrapolation from Figure 3 of Sun et al.).

C = 1% (since we could not find literature data we arbitrarily suppose a low incidence).

The probability that at least one event among A or B or C occur is the probability (P) of the union (U) of A and B and C minus the probability of their intersection (∩) as follow:

$P(A \cup B \cup C) = P(A) + P(B) + P(C) - P(A \cap B) - P(A \cap C) - P(B \cap C) - P(A \cap B \cap C) = 12\%$.

13.1.1. Derivation Cohort Sample Size

The size of the derivation cohort has been calculated to provide at least 10 events per variable that we expect to enter into the logistic regression model. Recording at least 120 RD events would allow around 12 predictor variables to be entered into logistic regression. Assuming an incidence of 12% of subjects with RD episodes and 12-variables for prediction rule, a sample size of 1000 subjects is needed for the derivation cohort.

The selection of 12 high risk variables for the prediction rule has been based on literature review[1,4,7,16,17,22]:

- Age > 65 y.
- Known or suspected sleep-disordered breathing (OSA, snoring, etc.).
- High risk surgery ≤ 24 hours.
- PCA or epidural or intrathecal therapy.
- Obese (BMI >30).
- Multiple opioid or concurrent CNS/sedating medication (benzodiazepines, sleep aids, muscle relaxant, etc.).
- High opioid dosage (>30mg oral morphine per day or equivalent).
- Major organ failure.
- Diabetes.
- Chronic heart failure or other significant cardiac disease.
- Smoke (> 20 packs per year).

- COPD or other significant pulmonary disease (including respiratory events before ward admittance).

13.1.2. Validation Cohort Sample Size

Since the derivation cohort will be 2/3 of the total sample size, the derivation cohort will be 1/3 (500 subjects) of the total sample size. Considering a 10% of withdrawals/dropouts/screening failure, the total sample size needed is 1650 subjects.

13.2. Data Analysis

A detailed description of the statistical methods will be contained in the Statistical Analysis Plan (SAP). Any change to the data analysis methods described in this section and/or the SAP will require an amendment only if it changes a principal feature of the study description. Any other changes to the data analysis methods will be described and justified in the Final Report or publication.

Based on the clinical practice in the opioid used and number of subjects enrolled per centre/country, an investigation of centre/country effect will be investigated including an independent variable for centres/country in the model as well as summary statistics if needed.

The choice of the imputation method for missing data will depend on the pattern of the missingdata and the type of the imputed variable.

The primary analysis will be performed on all subjects enrolled in the study and monitored with the Capnostream monitor and include all clinical outcomes that occur within the monitoring period(s) as for study design.

It is anticipated that SAS (SAS Institute Inc., Cary, NC, USA) will be used to perform all statistical analyses. Statistical tests will be based on a two-sided significance level of 0.05, and interaction effects will be evaluated at a significance level of 0.10. No adjustments for multiple comparisons will be performed. Additional exploratory analyses will be conducted as deemed appropriate.

The statistics above will be calculated by means of a GEE model as appropriate in order to take into account multiple events per subject and they will be reported together with the interval confidence (IC).

All assumptions for regression models will be assessed by viewing plots of the residual values.

Descriptive statistics will be used to summarize subject characteristics. This will include mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables. To compare subjects with and without the outcome, all categorical variables will be analyzed with the Chi-square test or the Fisher exact test or Cochran-Mantel-Haenszel test for trend for ordinal variables with 3 or more categories, as appropriate. Continuous variable parameter comparisons will be performed using t-test or Wilcoxon test according to the normal or non-normal distribution.

13.3. Primary Endpoint

At the end of data collection all subjects enrolled will be randomly assigned to the derivation set and the validation set at a ratio of 2 to 1. According to the outcome of the planned RD event rate monitoring, there could be the possibility to use the overall population as the derivation cohort. The validation sets will be performed using a bootstrapping method. A detailed description of the bootstrap method will be

reported in the Statistical Analysis Plan (SAP). Bivariate odds ratios (ORs) and 95% confidence intervals (95% CIs) will be estimated. The possibility of collinearity between categorical variables will be also tested. The logistic regression model will be performed using a backward stepwise selection procedure in which the presence of event will be the dependent variable. Independent predictors will be entered into the model if a significant association, defined as $p \leq 0.05$, will be identified from bivariate analysis and, to avoid over-fitted and unstable model the correlation coefficient between them should be less than 0.25.

The predictive risk score for RD will be calculated by multiplying each b coefficient (from the multivariate model by 10 and rounding to the nearest integer. The integers will then be added together to produce an overall RD risk score for each subject. The resulting continuous distribution of total risk scores across all subjects in the derivation set will be then stratified into 3 categories of points that grouped subjects according to the level of risk (low, medium and high risks). Model prediction performance will be assessed using calibration (the agreement between predicted and observed outcome) and discrimination (the ability to separate subjects with and without the outcome) and the R2 will be reported as an overall measure for discrimination and calibration. The Sensitivity and Specificity and the receiver-operating characteristic (ROC) curves will be used to visualize the overall accuracy of the model. The discriminatory performance of the model will be validated by comparing the ROC curve analysis in the derivation set with that in the validation set.

13.4. Secondary Endpoints

Comparisons on all categorical variables will be done using the Chi-square test or the Fisher exact test or Cochran-Mantel-Haenszel test for trend for ordinal variables with 3 or more categories, as appropriate. Continuous variable parameter comparisons will be performed using t-test or Wilcoxon test according to the normal or non-normal distribution.

The rate of events will be computed and reported separately for each group, together with their 95% confidence intervals. Rates will be then compared by means of either a mixed Poisson model or a negative binomial regression model (if overdispersion is present).

The Sensitivity and Specificity, Positve predictive value (PPV) and negative predictive value (NPV), and the ROC curves will be used to visualize the accuracy of the IPI algorithms at different cutoffs in predicting episodes.

13.5. RD Event Rate Monitoring

A monitoring tracking system of the RD event rate will be used during the study. The RD event rate will be evaluated on a regular basis and one of the following possible outcomes may result:

- Continue the study with a total of 1,650 subjects if the RD event rate falls within the Interval Confidence (IC at 95%).
- If the RD event rate is greater than IC up, the study could early terminate.
- If the RD event rate is lower than IC low but greater than or equal to 6% , all data collected will be used for derivation of the risk score.
- If the RD event rate is lower than 6%, the sample size will be re-estimated

If the sample size must be increased, Medtronic will determine whether or not to continue the study.

14. Ethics

14.1. Statement(s) of Compliance

This clinical study will be conducted in compliance with the Declaration of Helsinki (2013), laws and regulations of the countries in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan.

All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, EC/IRB approval and clinical study training.

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.

14.1.1. Ethics Committee / Institutional Review Board

Prior to enrolling subjects in this clinical study, each investigation site's EC/IRB 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 subjects and, if applicable, materials used to recruit subjects. EC/IRB 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/IRB 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/IRB. If they are members of the EC/IRB, written documentation is required stating that he/she did not participate in the approval process. If the EC/IRB imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the investigator for reporting to the EC/IRB.

Investigators must inform Medtronic of any change in status of EC/IRB approval once the investigation site has started enrollment. If any action is taken by an EC/IRB with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

14.1.2. 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 subjects will be enrollled 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.

14.1.3. Clinical Trial Insurance

The Patient Monitoring & Recovery business unit 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/IRB.

14.1.4. Subject 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 multiple countries, therefore reimbursement and indemnification will be addressed on a country specific basis in the study documents and site Clinical Trial Agreements.

Subjects 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 subject pays his/her co-payment for that treatment. No special compensation will be paid by the Sponsor.

15. Study Administration

15.1. 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 subject'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 subject 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/IRB approval letters and Clinical Trial Agreements, etc.) will be reviewed at each study center.

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/IRB approval and review of the study, maintenance of records and reports, and review of source documents against subject 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, letter, or on site at each enrolling study center.

The monitoring organization is the local sponsor with contact information as identified for each geography on the cover page, page 1 of this clinical investigation plan.

15.2. Data Management

15.2.1. Subject Data

Subject 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 or 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.

15.2.2. Device Data

Capnostream device memory data will be exported to a flash memory device for each subject. 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.

15.3. Direct Access to Source Data/Documents

15.3.1. 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 field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data on the electronic Case Report Form (eCRF). Direct access to subject medical files for source data verification (if applicable) will need to be granted and prepared prior to any monitoring visits.

15.3.2. 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. Independent 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 will allow inspections of the study site and documentation by Clinical Research and audit personnel from Medtronic or designee, EC/IRB, external auditors, or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the eCRFs. In order to do this, direct access to medical or clinical records is necessary.

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/IRB review (if applicable), and regulatory inspections.

15.4. Confidentiality

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

Subject 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 subject identification code will be assigned and used to allow identification of all data reported for each subject.

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 subject's privacy is guaranteed. Sites will maintain subject 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. The privacy of each subject and the confidentiality of his/her information must be preserved in reports when publishing any data.

15.5. 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 investigators to obtain approval from their EC/IRB, if applicable. Administrative amendments to the Clinical Investigation Plan will be submitted to the EC/IRB and appropriate regulatory authorities for notification, if applicable.

15.6. Record Retention

15.6.1. 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/IRB 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
- Subject Identification and Enrollment Log
- Signed, dated and fully executed informed consent forms

- Fully executed eCRFs and corrections

The investigator must retain the Investigator Site File, subject medical files and eCRF data in accordance with local law and regulations for a minimum period of 2 year (or longer if local laws require) after study completion.

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

15.6.2. 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/IRB approvals/notifications and regulatory approvals/notifications
- Signed Clinical Trial Agreements and signed agreements with third parties
- Insurance certificates, if applicable
- Medtronic and EC/IRC approved Informed Consents
- Site selection reports, site initiation reports and monitoring visit reports
- Adverse event reports
- Financial disclosures
- Fully executed eCRF data and corrections

15.7. Publication and Use of Information

The results of this clinical study will be submitted for publication. Publications and presentations referring to PRODIGY 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.

Based on the principle that Medtronic owns the data of this clinical study, a single investigation site may access and use the data provided by itself for scientific publications following prior approval by the Publication Committee.

Pooling data from several investigation sites for publication purposes, national projects and international projects all require prior approval from the Publication Committee.

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 marketing purposes, further research and development of devices or educational use.

The study sponsor will collect data in such way that no subject can be identified, and monitor study records.

Participating subjects will not be identified by name in any published reports about the clinical study.

15.8. Suspension or Early Termination

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the clinical study. Examples of reasons for potentially terminating the study may include, but are not limited to:

- If the RD event rate is greater than expected, the study could early terminate.
- If the RD event rate is lower than expected and sample size re-estimation indicates a need to increase the sample size., Medtronic will determine whether or not to continue the 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/IRB and the study subjects or their legal representative.

Medtronic, EC/IRB or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC/IRB, non-compliance to the Clinical Investigation Plan 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. The investigator shall then promptly inform the reviewing EC/IRB, if required, the study subjects 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/IRB, if applicable.

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

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

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17. Appendices

17.1. Appendix A: List of Anticipated Adverse Events

This is a list of respiratory related adverse events that may possibly be caused by or associated with opioid therapy and device related adverse events that may be possibly caused by the use of the devices required by this protocol.

Note that RD episodes alone, if subject is asymptomatic and no invasive actions are taken, are not considered as adverse events but would meet the primary endpoint of RD occurrence.

Table 5. Anticipated Respiratory Adverse Events

Narcotic overdose that required an Opioid reversal
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 Invasive mechanical ventilation
Upper airway obstruction requiring airway support measures (oral or nasal) such as intubation, LMA, or airway
Respiratory insufficiency/failure that would require a transfer to the ICU
Cardiopulmonary arrest
Death due to respiratory/pulmonary related complications
Other (free text that might capture aspiration, pneumothorax)

Table 6. Anticipated Device Related Adverse Events

AE	Definition
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.
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.

17.2. Appendix B: List of Medications

1.0 Medications		
1.1 Non-Opioid Analgesics ☐ NSAIDs ☐ 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. SSRI's** ☐ 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)

17.3. Appendix C: 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 < BMI < 40), well-controlled DM/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).