Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	**LIFEGUARD Study** – Continuous Respiratory Monitoring on the General Ward
Clinical Investigation Plan Identifier	MDT17026
Clinical Investigation Plan Version	2.0 June 19, 2019
Sponsor/Local Sponsor	[redacted]
Document Version	Version 1.1, July 12, 2019

[redacted]

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1. Version History

Version	Summary of Changes	Author(s)/Title
Version 1.0	Not Applicable, New Document	[redacted]
Version 1.1	Updated accordingly to align with CIP version 2.0	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CIP	Clinical Investigation Plan
CS	Capnostream
EC	Ethics Committee
$EtCO_2$	End Tidal CO_2
EWS	Early Warning Scores
FAS	Full Analysis Set
FN	False Negative
FP	False Positive
GEE	Generalized Estimating Equation
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICH E3	ICH guideline E3: Structure and content of clinical study reports
ICH E6	ICH guideline E6: Guideline for Good Clinical Practice
ICH E9	ICH guideline E9: Statistical principles for clinical trials
ICU	Intensive Care Unit
IPI	Integrated Pulmonary Index
NPV	Negative Predictive Value
OC	Oracle Clinical
OR	Odds Ratio
PPS	Per Protocol Set
PPV	Positive Predictive Value
RC	Respiratory Compromise
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOPs	Standard Operating Procedure
SpO_2	Pulse Oximetry
TLF	Tables, Listings, and Figures
TN	True Negative
TP	True Positive

3. Introduction

Early postsurgical period is associated with high incidence of postoperative pulmonary complications, including pneumonia, aspiration pneumonitis, respiratory failure, re-intubation within 48h, weaning failure, pleural effusion, atelectasis, bronchospasm, and pneumothorax.
The most frequent severe postoperative respiratory complications is respiratory failure, defined as unexpected tracheal re-intubation, need for postoperative mechanical ventilation, postoperative acute lung injury and acute respiratory distress syndrome.
Current standard of care for respiratory monitoring of hospital ward high risk patients, such as those receiving opioid therapy, is intermittent documentation of SpO_2 value. Respiratory rate (RR) is often determined by clinician assessment though manual inaccurate respiration counts.
There are no data on the real incidence and severity of potential RC markers and their correlation with cardiopulmonary or other complications in European postsurgical patients. A pilot study on this topic could be useful to collect information on the utility of continuous SpO_2 and capnography monitoring in this setting and to develop future clinical evidence.
The main purpose of the LIFEGUARD study is to quantify the incidence and the severity of postoperative RC markers on high risk postsurgical patients on a general ward.
This SAP is based on Protocol 2.0, 19 Jun 2019 titled, "**LIFEGUARD Study** – Continuous Respiratory Monitoring on the General Ward". The SAP has been prepared in agreement with Medtronic internal procedures and using the CONSORT Flow diagram1 and International Conference on Harmonization (ICH) guidelines ICH E3, ICH E6 and ICH E9 as guidelines.

4. Study Objectives

4.1. Primary Objective

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

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

- $SpO_2 \leq 90\%$ for ≥ 3 minutes (or SpO2 ≤ 90% for < 3 min with an action taken);
- RR ≤ 8 or ≥ 22 bpm for ≥ 3 minutes (or RR ≤ 8 or ≥ 22 bpm for < 3 min with an action taken);
- $EtCO_2 \leq 15$ or ≥ 60 mmHg for ≥ 3 minutes (or etCO2 ≤ 15 or ≥ 60 mmHg for < 3 min with an action taken);
- Apnea episode lasting > 30 seconds.

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

- $SpO_2 \leq 90\%$ for ≥ 3 minutes (or SpO2 ≤ 90% for < 3 min with an action taken);

- RR ≤ 8 or ≥ 22 bpm for ≥ 3 minutes (or RR ≤ 8 or ≥ 22 bpm for < 3 min with an action taken).

4.2. Secondary Objectives

The study secondary objectives are the followings:

1. To compare the two study Phases (see Section 7.1.1) in terms of primary endpoint incidence;
2. To compare the two study Phases in terms of respiratory AEs and SAE incidence, numbers of ICU transfers and related length of stay, Code blues and RRT responses;
3. To evaluate the impact of introducing continuous monitoring devices connected to a remote monitoring platform on the clinical workflow, defined as the rate of clinical early interventions performed by nurse staff to prevent a potential AE (e.g. patient stimulation, Jaw thrust maneuver, oxygen administration started or increased, medication change, etc.);
4. To evaluate the impact of introducing continuous monitoring devices connected to a remote monitoring platform on clinical staff's workflow, defined as nurses' satisfaction related to the monitoring system;
5. To characterize the predictive values of $EtCO_2$, RR, SpO_2, plethysmography-derived RR, IPI^2 and EWS in respect to respiratory and other SAE.

Related secondary objectives are:

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

5. Investigation Plan

5.1. Study Design

This is a prospective, post-market interventional, pilot study. Approximately 210 patients will be enrolled in two European centers. At least 15 subjects per month are expected to be enrolled at each participating center. Each subject will be in the study for a maximum period of 72 hours.

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

5.2. Inclusion/Exclusion criteria

All inclusion and exclusion criteria stated in sections 7.3 and 7.4 from CIP, must be met for subjects to be eligible for consent/enrollment inclusion in the study.

The investigator will 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.

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

5.3. Overall study design and plan-description

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

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

During **Phase I** the alarm feature of the monitoring devices will be silenced, and the screen information blinded. A regular check during the monitoring period should be completed to ensure the $EtCO_2$ filter line and SpO_2 sensors are appropriately fitted on the subject.

During **Phase II** the medical staff will be instructed to respond to alarm feature of the monitoring devices and their screen will be open. A guideline will be created to instruct the nurses in responding to alarms and changes in the monitored parameters on which the nurses will be trained on.

A Flow-chart to schematize the disposition of subjects during the study is presented in Figure 1.

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

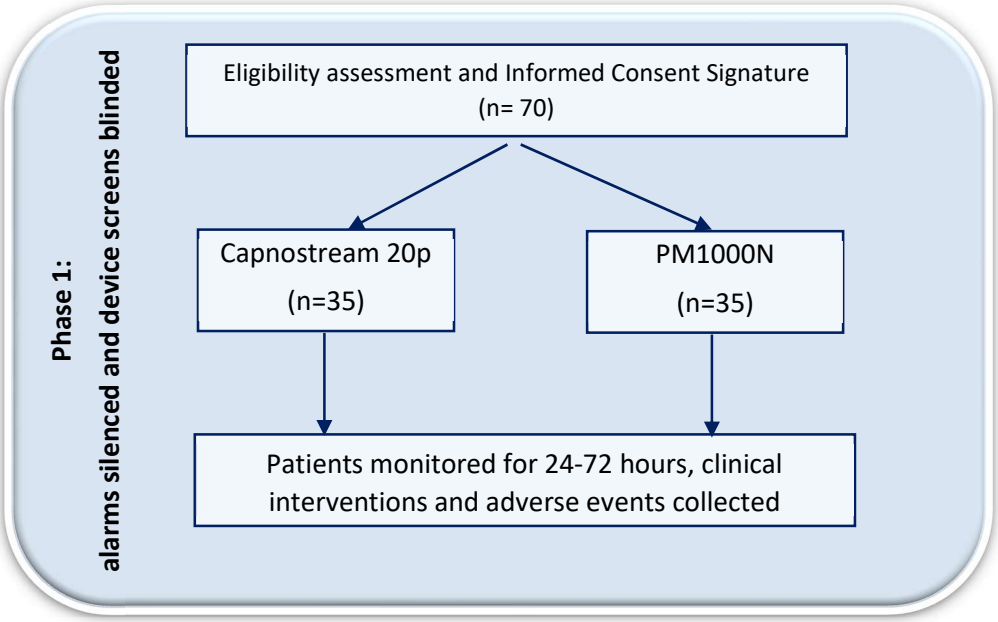
Enrollment at any single site will be limited to 50% (approximately 105 subjects) to ensure poolability of the data across sites and reduce potential bias. Additional methods incorporated to minimize potential bias include the following:

- Systematic identification of potential subjects via screening;

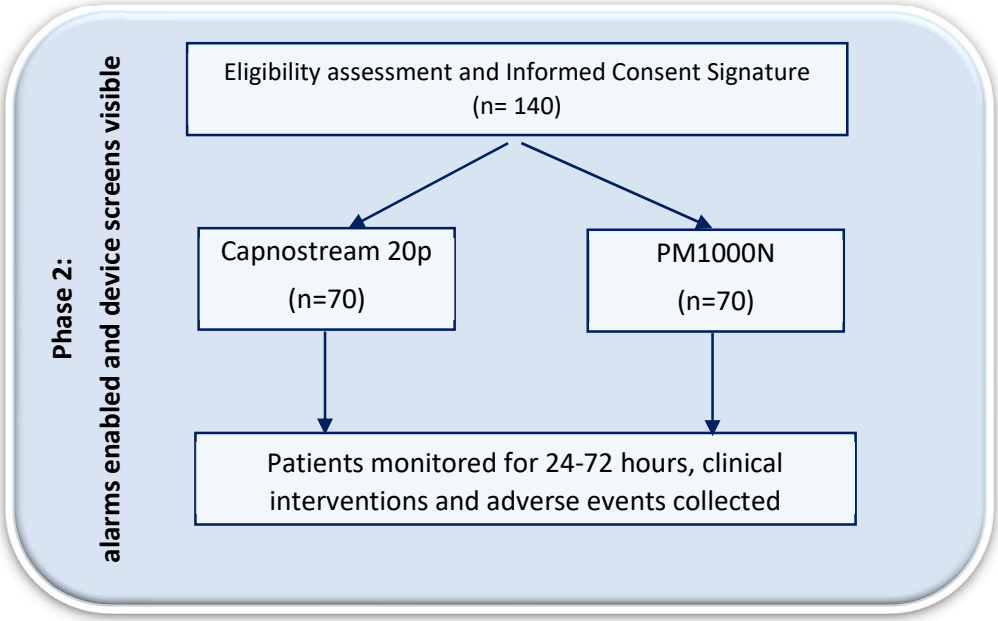
- Standard procedures and data collection requirements with a common electronic database for all sites;
- Random allocation to monitoring device.

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

Figure 1 – Study Flow-chart



One-month minimum period for unblinded device familiarization



Data collection requirements are summarized in Table 1.

Table 1 - Data Collection Requirements

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

6. Determination of Sample Size

The sample size calculation is based on primary endpoint and it was estimated using data from previous studies with a precision-based calculation. Recent data on post-surgical patient have shown a proportion of patient with the RC markers for the $SpO_2 \leq 85\%$ for ≥ 3 minutes at 13%[3] and for RR ≤ 8 or ≥ 22 bpm for ≥ 3 minutes at 1.4%[4] in patients undergoing opioid therapy. Using this information, a minimum proportion of 10% of patients with RC markers with a sample size of 182 subjects will be able to obtain a 95% confidence level with a precision of 5% (ranging from 5% to 10%) and a power of at least 0.80 defined as the probability of achieving the desired precision. Considering a 10% withdrawal or potential dropouts and a potential attrition rate to monitoring compliance of 5% a total of approximately 210 subjects will be enrolled. This cohort will be used prospectively for the blinded and not blinded phase with a ratio 1:2 respectively to minimize not blinded monitored subjects. The blinded phase will enroll

70 subjects randomly allocated 1:1 in the Capnostream 20p and PM1000N arms while the not blinded phase will enroll 140 subjects with same randomized schedule.

7. Statistical Methods

7.1. Study Subjects

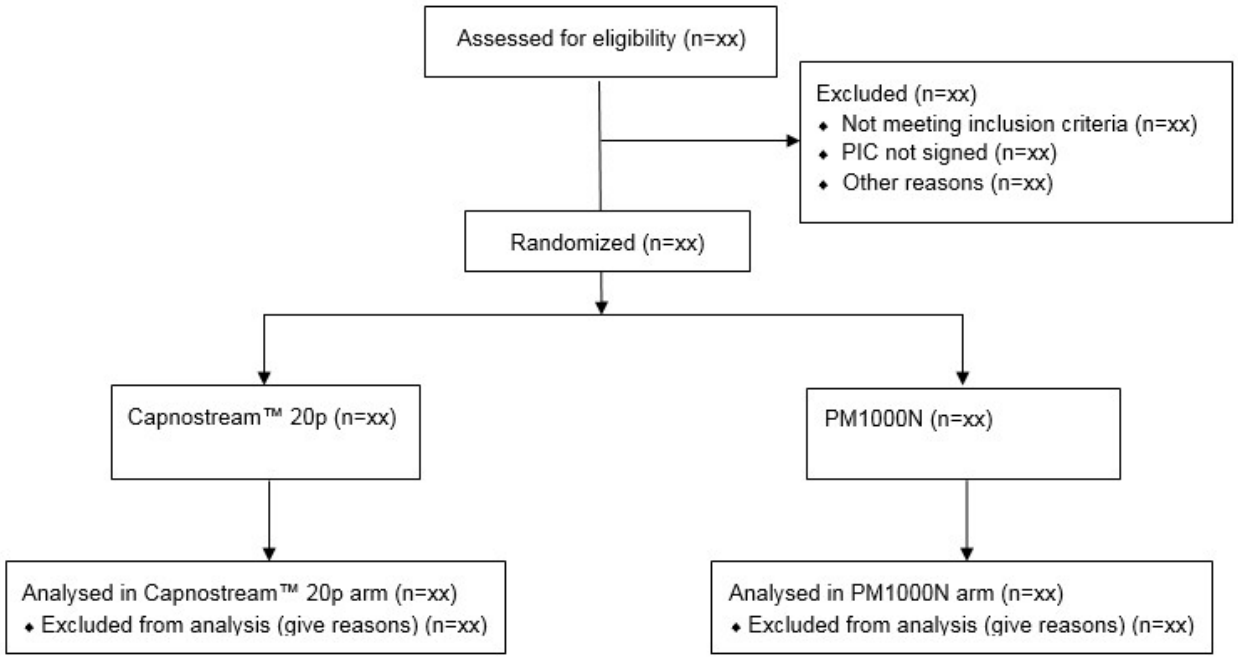
The target study population consists of post-surgical subjects of adult age at high risk of developing respiratory and cardiovascular events on the hospital ward.

7.1.1. Disposition of Subjects

Disposition of subjects will be reported following the CONSORT Flow Diagram1, even though this is a prospective, post-market interventional, pilot study and no comparisons between arms will be performed. Number of individuals at each stage of study (number of total assessed for eligibility, number of patients in FAS and number of patients in PPS) will be reported for both Capnostream™ 20p and PM1000N. Reason for not participation at each stage will be reported where known.

Table 2 - Number of Subject Screened and Enrollments by Site and Ward

Figure 2 – CONSORT Flow diagram of Patient Disposition



7.1.2. Clinical Investigation Plan (CIP) Deviations

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, with the associated visit of the deviation, the type of the deviation and the reason for the deviation.

All Deviations will be reviewed and classified by the clinical study team and the following tables will describe study deviations.

Table 3 - Protocol Deviation by Reason - FAS

Table 4 - Protocol Deviation by Visit - FAS

Listing 1 - Other deviations – FAS

7.1.3. Analysis Sets

The following patient sets will be used for the analysis:

- The Full Analysis Set (FAS) includes all patients actively enrolled in the study, who signed Informed Consent Form (ICF), fulfilled the inclusion/exclusion criteria and monitored by CS20p or PM1000N. The FAS will be used to describe both baseline characteristics and safety outcomes of the study population;
- The Per Protocol Set (PPS) includes all patients in the FAS, without major protocol deviations, who have at least 24 hours of monitoring *effective time*[1]. The PPS will be used to describe baseline characteristics of the study population and to evaluate the primary and secondary endpoints. Patient with poor quality of device data, defined as having less than 90% of time continuously monitored, will be included or excluded from the PPS, as appropriate.

The following table shows how each population set will be used for analyses:

Population set	Baseline assessment	Primary and Secondary Endpoint #1	Secondary Endpoints #2, #3, #4 and #5	Safety AE Death
FAS	√		√	√
PPS	√	√	√	

For those patients who have less than 24 hours or poor quality of device data monitoring or who withdrew, the analyses will include all data up to the point of their last data collection only for FAS population.

An additional set could be created during the analysis phase, in case necessary to investigate on a particular subgroup of patients.

[1] Effective time is the cumulative time with valid recorded data. This aimed to filter out periods of time where the patient was not connected to the Capnography cannula or pulse-ox sensor, but recording was on-going (the patient was not monitored during this time).

7.2. General Methodology

For FAS and PPS descriptive statistics will be used to summarize patient characteristics. This will include mean and standard deviation, minimum, maximum and median with the interquartile range [IQR] for continuous variables and counts and percentages for categorical variables. Summary statistics will be reported with maximum 2 decimals, as appropriate. Comparisons between phases have been performed using Wilcoxon's Test for continuous variables, while comparisons of categorical variables have been performed by means of the Chi-square test or Fisher exact test for extreme proportions, as appropriate. Statistical tests were based on a two-sided significance level of 0.05.

Analysis for specific objectives have been stated in the corresponding sections (7.9.1 and 7.9.2).

When comparison of clinical primary outcomes is conducted the propensity score method could be used to control for biases and confounding which may be due to the nature of this study.

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.

7.3. Center Pooling

The study will involve more than one site and a center impact on primary outcome could be investigated. A description on primary outcome by site with 95% confidence intervals for each center will be provided, as appropriate. Additional exploratory analysis on baseline characteristics could be performed to check potential difference on primary outcome among sites.

7.4. Handling of Missing, Unused, and Spurious Data and Dropouts

Since the impact of missing data is expected to be small, no multiple imputation method for missing data is planned. However, the issue of missing data could arise; the choice of the imputation method for missing data will depend on the pattern of missing data and the type of the imputed variable.

The missing device data will not be imputed and the minimal device data requirement for inclusion is at least 90% of time continuously monitored.

Outliers and influential observations will be identified via graphical plots. Once identified outliers, or influential observations the study team will be informed and according to their decision the analysis for primary endpoint will be repeated excluding the outliers.

7.5. Adjustments for Multiple Comparisons

No adjustments for multiple comparisons or multiple look at data will be performed.

7.6. Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics, medical history and vital signs variables for both FAS and PPS. This will include mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables.

To compare characteristics between phases the Chi-Square' Test will be used for categorical variables and the Wilcoxon's Test will be used for continuous variables.
Demographic and Baseline variables will be collected through OC and described with Tables, Listings and Figures as appropriate.

Table 5 - Subject Demographics and baseline characteristics– FAS

Table 6 - Subject Demographics and baseline characteristics – PPS

Table 7 - Subject Medical History – FAS

Table 8 - Subject Medical History – PPS

Table 9 - Subject Vital Signs – FAS

Table 10 - Subject Vital Signs – PPS

7.7. Treatment Characteristics

Extent of exposure in the population is characterized according to the duration of the study with routine monitoring.

Duration of **Monitoring Exposure** will be measured in minutes from the start of the monitoring through and including the time of monitoring end: Duration of monitoring exposure (minutes) = (End monitoring date/time – Start monitoring date/time). Extent of exposure will be presented in a summary table and supporting data listing.

Duration of **Study Exposure** will be measured in days starting from the point of enrollment (informed consent completed and inclusion/exclusion criteria confirmed per the screening evaluation) through and including the time of study exit: Duration of study exposure (days) = (Study Exit date – date of enrollment). Extent of study exposure will be presented in a summary table and supporting data listing.

Descriptive statistics will be used to summarize treatment characteristic variables for both PPS and

for FAS. This will include mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables.

Table 11 – Monitoring Exposure – FAS

Table 12 - Monitoring Exposure – PPS

Table 13 – Study Exposure – FAS

Table 14 - Study Exposure – PPS

7.8. Interim Analyses

No interim analyses have been planned.

7.9. Evaluation of Objectives

7.9.1. Primary Endpoint

The Primary Endpoint of the Study is to quantify the incidence of RC markers in high risk postsurgical patients, using a system comprised of two continuous monitoring devices, connected to a remote monitoring platform. The proportion and rate of "At least one RC marker" event will be calculated and reported.

The "At least one RC marker" event is defined as the occurrence of at least one of the following RC markers:

1. $SpO_2 \leq 90\%$ for ≥ 3 minutes (or SpO2 ≤ 90% for < 3 min with an action taken);
2. RR ≤ 8 or ≥ 22 bpm for ≥ 3 minutes (or RR ≤ 8 or ≥ 22 bpm for < 3 min with an action taken);
3. $EtCO_2 \leq 15$ or ≥ 60 mmHg for ≥ 3 minutes (or etCO2 ≤ 15 or ≥ 60 mmHg for < 3 min with an action taken);
4. Apnea episode lasting > 30 seconds.

For patients monitored by PM1000N, only RC markers #1 and #2 will be considered.

RC determination will be assessed by a physician belonging to the "other" site (cross assessment by the sites). This assessment will be made by the analysis of both device and clinical data for each patient. For each patient all potential RC episodes will be derived using the Detection Tool (see Section 10.1) and will be submitted to the other site's physician in order to adjudicate the potential RC episodes starting from episodes most likely to be RC. The adjudication will stop at the first RC occurring per patient.

The Events' rates will be computed as (total number of "At least one RC marker" event)/(total number of time-person in PPS) and will be reported separately for each arm and phase of the study. Events' rates will be displayed together with their 95% confidence interval (95%CI).

If the number of episode per patient result unbalanced, adjusted rates will be reported using the GEE model, together with their 95% confidence interval (95%CI).

If appropriate, also the events' rates for each RC marker will be reported separately, for each arm and phase of the study.

7.9.2. Secondary Endpoints

The secondary endpoints are:

1. To compare phases in terms of Primary endpoint incidence;
2. To compare phases in terms of respiratory and SAE incidence, number of ICU transfers and related length of stay, Code blues and RRT responses.
3. To evaluate the rate of clinical early interventions performed by nurse staff to prevent a potential AE, introducing continuous monitoring devices connected to a remote monitoring platform;
4. To evaluate the nurses' satisfaction related to the monitoring system introducing continuous monitoring devices connected to a remote monitoring platform;
5. To establish the Predictive values of $EtCO_2$, RR, SpO_2, plethysmography-derived RR, IPI^2 and EWS in respect to respiratory and other SAE.

In order to evaluate secondary **endpoints #1 and #2**, the incidence of events will be reported together with the comparison between phases, by means of the Chi-square test or Fisher exact test for extreme

proportions, as appropriate. If the monitoring/study exposure results different between phases, also the rates of events will be reported, together with the 95% Poisson Confidence Intervals. The Poisson regression model will be used to calculate the Incidence Rate ratio (IRR), with the d-scale option.

For **endpoint #3**, the rate of clinical early interventions will be calculated as (number of early interventions)/(total time-person in FAS) and it will be reported together with the 95% Poisson Confidence Interval.

Early interventions include, as defined in CRF (Monitoring Period):

1. Stimulated subject to breathe;
2. Repositioned/opened airway;
3. Held or reduced Respiratory Depressive (RD);
4. Added or increased supplemental oxygen;
5. Ventilation support;
6. Other

Endpoint #4 will be evaluated reporting a summary of the nurses' satisfaction answers.

To identify the predictive values for $EtCO_2$, RR, SpO_2, plethysmography-derived RR, IPI^2 and EWS, which can predict respiratory and other SAE, a sensitivity analysis will be performed (**endpoint #5**), and the following parameters will be reported, for each RC marker:

1. $\text{Sensitivity} = \frac{(\#\text{ of clinical events "Yes" and with RC marker "Yes"})}{(\#\text{ of clinical events "Yes"})} = \frac{TP}{(TP+FN)}$
2. $\text{PPV} = \frac{(\#\text{ of clinical events "Yes" and with RC marker "Yes"})}{(\#\text{ of events with RC marker "Yes"})} = \frac{TP}{(TP+FP)}$

RC marker	Clinical Events		Total
	Yes	No	
Yes	(TP)	(FP)	(TP + FP)
No	(FN)	(TN)	(FN + TN)
Total	(TP + FN)	(FP + TN)	(TP+TN+FP+FN)

To perform this analysis, a temporal window to find RC markers that could be associated with a clinical event will be defined (for example ± 1 minute from the event).

Due to the impossibility to identify the true negatives (TN), both the specificity and the NPV could not be calculated.

7.10.Safety Evaluation

Adverse events in the Full Analysis Set will be presented in summary tables and supporting data listings. Secondary objectives described in Section 7.9.2 include safety evaluations and will be summarized as already described.

Adverse events will be presented using the MedDRA coding and with the following summary tables and supporting data listing:

Table 15 – Adverse Event by Primary System Organ Class and Preferred Term – FAS

Table 16 - Adverse Event Seriousness and Relatedness – FAS

Table 17 - Individual Adverse Events for which Sponsor and Investigator disagreed – FAS

Listing 2 - Individual Adverse Events – FAS

Table 18 - Death Summary – FAS

Listing 3 - Death – FAS

7.11. Health Outcomes Analyses

No specific health outcomes' analyses were planned in the protocol, except for those considered in the secondary objectives.

7.12. Changes to Planned Analysis

If the pre-defined cut-off of 24 hours of monitoring needed for the PPS will be unreachable, future modifications of this cut-off could be considered or, alternatively, a new definition of the populations could be done. Similarly, the 90% cut-off of time continuously monitored could change, accordingly to the study population, as appropriate.

Both the above changes could be applied in order to analyze the higher number of patients from the enrolled ones.

8. Validation Requirements

To ensure the quality of the results provided for the study in the form of tables, listings and figures, and the derived datasets the following processes are used:

- Statistical programming and analysis will be done by qualified programmer(s), engineer(s) or statistician(s) following applicable procedures and best practices.
- The derived datasets will be validated by a second programmer or statistician.
- The tables will be validated by a second programmer or statistician.
- Statistical results will be reviewed and confirmed by a second statistician.

The entire set of tables, listings, and figures (TLF) will be 100% checked for accuracy, completeness, and consistency prior to inclusion in the final clinical study report. According to Medtronic SOPs the level II validation (the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output) will be implemented for Analysis Datasets and TLFs.

9. References

1. www.consort-statement.org/

2. Ronen M., Smart respiratory monitoring: clinical development and validation of the IPI™ (Integrated Pulmonary Index) algorithm, Journal of Clinical Monitoring and Computing, pp 1-8 mar 2016
3. Sun Z, Sessler DI, Dalton JE, et al. Postoperative Hypoxemia Is Common and Persistent: A Prospective Blinded Observational Study. Anesth Analg [Internet] 2015 [cited 2015 Sep 25];121(3):709–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26287299
4. Mccarter T, Shaik Z, Scarfo K, Thompson LJ, Rt R. Capnography Monitoring Enhances Safety of Postoperative Patient-Controlled Analgesia. 2008;(June):3–9.

10. Statistical Appendices

10.1. Detection Tool

The Detection Tool analyzes each patient's monitoring using an algorithm based on the device episodes thresholds as stated in the primary endpoint. The Detection Tool provides for each patient multiple Episodes. Since there could be multiple episodes in a short time period around each Episode, the Detection Tool is set to aggregate episodes with at most 30 minutes time difference between them in one file. In addition, the episodes file consists of time window of 30 min before and after the first and last episode.