



Respiratory depression in low acuity hospital settings—Seeking answers from the PRODIGY trial



Ashish K. Khanna^{a,*}, Frank J. Overdyk^b, Christine Greening^c, Paola Di Stefano^d, Wolfgang F. Buhre^e

^a Center for Critical Care and Departments of General Anesthesiology and Outcomes Research, Cleveland Clinic, Cleveland, OH, United States

^b Roper St Francis Health System, Charleston, SC, United States

^c Medtronic Minimally Invasive Therapies Group, Boulder, CO, United States

^d Medtronic Regional Clinical Center, Rome, Italy

^e Department of Anesthesiology and Pain Therapy, University Medical Center Maastricht, the Netherlands

ARTICLE INFO

Available online xxxx

Keywords:

Respiratory depression

Ward

Cardiorespiratory monitoring

Continuous

Capnography

Prediction

ABSTRACT

Predicting episodes or severity of cardiorespiratory decompensation has proved to be challenging in patients with stable surgical or medical conditions, recovering on the general care floor (ward). Critical cardiorespiratory events on hospital floors may be prevented by early detection of deterioration using continuous, electronic cardiorespiratory monitoring (CEM). The PRediction of Opioid-induced Respiratory Depression In Patients Monitored by capnoGraphY (PRODIGY) trial investigates CEM using pulse oximetry and capnography in 1650 patients at 16 centers in North America, Europe, and Asia ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02811302) Identifier: NCT02811302). The primary goal of the study is to derive a risk prediction score for respiratory depression (RD) on the ward. The validation-derivation cohort design will derive this score from RD detected by continuous, blinded, multiparameter cardiorespiratory (heart rate, respiratory rate, end tidal carbon dioxide, and pulse oximetry) monitoring of patients on the ward receiving parenteral (including epidural) opioids for primary analgesia. This review provides a comprehensive synopsis on respiratory compromise in lower acuity hospital settings (ward) and describes the protocol of the PRODIGY trial as a means to enable prediction and early response to these events.

© 2018 Elsevier Inc. All rights reserved.

1. Scope of the problem

Mortality within 30 days after surgery is currently the third leading cause of death in the United States [1, 2]. The most common cause of this 30-day postoperative mortality not surprisingly is cardiorespiratory complications. The Agency for Healthcare Research and Quality (AHRQ) recently rated postoperative respiratory failure as the fourth most common patient safety event [3]. The incidence of respiratory

depression (RD), based on varied definitions and criteria ranges from as little as 0.3% to 17% [4]. Indeed, while we have made significant improvements in intraoperative safety under anesthesia, the same cannot be assumed for the postoperative period.

The medical or surgical general care floor (ward) is a lower acuity hospital setting where patients are deemed to have achieved a point of stability in their disease pathology. Therefore, they are presumed to have a sufficiently low risk of developing a serious adverse event. Yet 41% of in-hospital cardiac arrests occur on the ward, and outcomes are invariably catastrophic [5]. The adjusted survival rate for patients suffering a cardiac arrest on a medical surgical ward is 0.106, lower than the survival rate for patients arresting in an intensive care unit (0.144) [5].

2. Predicting respiratory depression

Risk factors for developing RD have been widely studied in literature, specifically for post-surgical patients. These include sleep disordered breathing, obesity, advanced age, post-surgical status, increased opioid dose requirement, concomitant use of other sedating medications, comorbidities including pulmonary or cardiac disease, opioid use via patient controlled analgesia systems and smoking [6–10].

Despite these known risk factors, prediction of postoperative respiratory decompensation remains a challenge. Residual anesthetic gases,

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; APSF, Anesthesia Patient Safety Foundation; ASA, American Society of Anesthesiologists; CEC, Clinical Events Committee; DNR, do not resuscitate; ERAS, early recovery after surgery; CIP, clinical investigational plan; DMC, Data Monitoring Committee; eCRF, electronic clinical report form; EC/IRB, Ethics Committee/Institutional Review Board; FAS, full analysis set; HR, heart rate; ICU, intensive care unit; IPI, integrated pulmonary index; mFAS, modified full analysis set; NPV, negative predictive value; OIRD, opioid induced respiratory depression; OIVI, opioid induced ventilatory insufficiency; ORADE, opioid-related adverse drug event; PCA, patient controlled analgesia; PACU, post-anesthesia care unit; PPV, positive predictive value; PR, pulse rate; ROC, receiver-operating characteristic; RD, respiratory depression; RR, respiratory rate; SAP, statistical analysis plan.

* Corresponding author at: Center for Critical Care, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Avenue, G-58, Cleveland, OH 44195, United States. Tel.: +1 513 658 5866; fax: +1 216 444 7360.

E-mail address: ashish@or.org (A.K. Khanna).

URL: <http://www.or.org/>.

muscle relaxants, and narcotics may contribute to RD in the post-anesthesia care unit (PACU). On the other hand, impaired respiratory mechanics and altered physiology, baseline co-existing respiratory diseases, and secondary insults which do not allow for effective gas exchange across the alveolar capillary membrane are often responsible for respiratory compromise in the Intensive Care Unit (ICU). However, patients rarely die of sudden, undetected RD in either the PACU or the ICU. When analysing the causes of in hospital cardiac arrest, Perman and co-workers reported that 49% of patients on the ward had a respiratory cause, and this was significantly higher than patients in an ICU, where respiration is both controlled and closely monitored [5]. The most obvious reason for this may be a difference in the nature of vital sign monitoring, which is continuous and multi-parameter in the ICU but limited to 'spot-checks' every few hours on the ward. While rapid response systems are in place on the ward, these are critically dependent on real time detection of patient deterioration. However, the lack of continuous monitoring on the ward effectively impairs this afferent or detection loop of rapid response systems. This is responsible for the unproven efficiency of rapid response systems to reduce morbidity and mortality on the ward [11, 12].

Recently, Sun et al. monitored continuous postoperative oxygen saturation in non-cardiac surgical patients for the first 48 h of the post-surgical period [13]. This monitoring started once the patient left the PACU or the ICU and reached the regular nursing floor. Importantly, bedside care providers were blinded to this oximetry. Nurses continued their routine checks on vital signs every 4 h per protocol. Results showed that postoperative hypoxemia was common and prolonged. For example, 20% of patients demonstrated an average of 10 min of saturation <90% per hour over their entire hospitalization. Rather shockingly, 90% of serious hypoxemic episodes (saturation <90% for ≥ 1 full hour) were missed by nurses charting routine vital sign monitoring at four-hour intervals [13]. Therefore, these hypoxemic events were serious and were undetected based on standard monitoring protocols. Further analysis of this cohort also showed that not only is post-operative hypoxemia common, undetected, prolonged and serious, it is also extremely difficult to predict. Surprisingly, an escalating risk using the STOP-BANG scoring system (a validated measure of obstructive sleep apnea risk) was not associated with the incidence or duration of postoperative oxygen desaturation [14]. In addition, the type of narcotic (long vs. short-acting) used in patient controlled analgesia (PCA) systems was not associated with the risk of hypoxemia in the post-operative period [15]. Thus, patients with a higher risk of obstructive sleep apnea and those on continuous long-acting intravenous narcotics, identified as at high risk of RD, could not be reliably predicted to have respiratory compromise based on readily available tools to this effect.

3. Opioids and respiratory depression

Opioid therapy is a commonly used treatment for acute post-surgical pain on the hospital ward. In addition, many non-surgical patients admitted in the hospital are also exposed to opioids. Opioid induced respiratory depression (OIRD), also known as opioid induced ventilatory insufficiency (OIVI), has been implicated as a significant cause of undetected and preventable deterioration for patients in ward settings [16]. In recent years there have been increasing concerns over unmonitored mortality and morbidity in patients during opioid therapy for acute pain [4]. Up to 80% of patients who received opioid analgesics experience Opioid-Related Adverse Drug Events (ORADEs) [11]. In post-surgical patients, ORADEs have been shown to significantly increase a patient's hospital length of stay and related costs. Improper patient monitoring has been reported by the Joint Commission as one of the main causes of ORADEs [11]. A recent multivariate analysis of an administrative database analysis revealed that opioids and sedatives are independent, yet additive risk factors for cardiac and or respiratory arrest on the general care floor [17]. A significant number of these arrests occurred in patients electively admitted for surgery, and with few

comorbidities. A closed claims analysis examined postoperative opioid induced RD and found that a clear majority of these patients unfortunately suffered death or severe brain damage because of the respiratory event [18]. As previously described obstructive sleep apnea risk score was a poor predictor in that only 4% of the patients had an elevated STOP BANG score [18].

4. Unprecedented respiratory events and critical care resources

Unplanned ICU admissions may have a respiratory indication in 17–47% of cases. The rate of these admissions is much higher when examining postoperative pulmonary complications in particular. There is reasonable reason to believe that at least some of these admissions may be unavoidable [19–22]. Data from the United States indicates excessive and unnecessary ICU capacity strain secondary to the burden of preventable ICU admissions. More large hospital systems report an inability to immediately provide a bed when required, with occupancy rates projected to increase in the coming years [23–25].

Straining ICU resources sets up a domino effect whereby the need to create more ICU beds to accommodate unplanned admissions from the floor, prompts premature discharge of other less ready patients, a large fraction of whom come back as readmissions [26–29]. ICU admissions refusals also occur when ICUs are operating at 100% capacity. Therefore, other patients with who require critical care services have a lower probability of admission [30, 31]. This in turn relegates borderline patients to the floor where they may be more likely to deteriorate and hence add to the vicious cycle of ICU capacity strain. Patients derive the greatest benefit from ICU management in the early stages of deterioration, and hence early ICU admission is important and necessary. These delays, particularly those in excess of 6 h, are associated with an increase in ICU mortality and hospital length of stay [32–36]. There is also evidence to suggest less patient physician interaction time, poor documentation and less rigorous adherence to quality measures in acute care areas when confronted with pressures of new floor admissions [37–40].

5. Preventive interventions for respiratory events

Lee et al. concluded that almost all opioid induced RD events on the ward were deemed preventable with better monitoring and response [18]. Forty-two percent of RD episodes in this analysis occurred within 2 h of the last nursing check. This is a common scenario wherein during a spot-check a patient is awake and instructed to take deep breaths till a satisfactory vital sign is recorded. However, as soon as the care provider leaves the room, the patient may obstruct their airway, hypoventilate and desaturate in repetitive cycles until they are unable to compensate and suffer a respiratory arrest. If undetected, this inevitably deteriorates into a full blown cardiopulmonary arrest [18]. A rapid response activation at this stage is often too late to institute any effective measures to reverse the crisis.

Our inability to predict and detect respiratory compromise on the ward suggests improved monitoring may be a solution [41, 42]. Improved monitoring should include continuous automated multi-parameter cardiorespiratory vital signs monitoring. However, vital sign parameters combination, best suited to continuous monitoring and early detection of respiratory decompensation are a matter of debate.

Respiratory events do not occur in isolation. Tachycardia and hypoxemia commonly co-exist and often culminate in hypotension which is strongly associated with myocardial injury and death [43, 44]. As might thus be expected, it is well established that vital signs deteriorate 6–12 h before cardiac and respiratory arrests occur [11, 45–47] – which is the basis for having hospital rapid-response teams which undoubtedly save lives [11, 12, 43–47]. Further, a recent study suggested respiratory rate does not contribute meaningfully to early detection of deterioration for patients monitored with continuous oximetry [48].

6. PRODIGY – rationale

Currently, there are no universally accepted guidelines to direct effective and safe assessment and monitoring practices for patients receiving in-hospital opioid analgesia. Oxygen desaturation detected by pulse oximetry may not be a sufficiently early warning of respiratory decompensation in the presence of supplemental oxygen, which is commonly administered with or without clinical rationale. Growing evidence supports the use of capnography for earlier and more reliable warnings of RD in postoperative patients in the general ward, when compared with pulse oximetry [42, 49]. It has been demonstrated that the value of RD detected by capnography is significantly increased compared to RD detected by oxygen desaturation alone in post-surgical patients using opioids as a part of patient controlled analgesia systems [41]. The Anesthesia Patient Safety Foundation (APSF) recommends continuous monitoring of ventilation using a suitable technology (i.e. capnography) in addition to continuous monitoring of oxygenation for all patients receiving opioid therapy in the postoperative period, especially when supplemental oxygen is administered [28]. The gap in knowledge is furthermore evident in non-surgical patients, where there is no existing data in literature that can identify the extent of RD or needed monitoring that would be considered adequate. Therefore, the need of a simple tool to stratify patients at risk to develop opioid induced RD while on the general care floor has been underlined and emphasized by several studies [1, 4, 13, 41].

PRODIGY is a multicenter, prospective study designed to derive and validate a risk assessment tool derived from a combination of continuous respiratory monitoring and clinical data that can identify patients at greater risk of RD episodes when receiving parenteral opioid therapy on the hospital ward. The trial is registered at www.clinicaltrials.gov (NCT02811302). Recruitment for PRODIGY started in April 2017 and ended in April 2018. This clinical study is conducted in compliance with the Declaration of Helsinki, 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.

This risk assessment tool will effectively identify patients at risk of experiencing respiratory depression while receiving parenteral opioid analgesia.

The primary outcome of PRODIGY will be:

1. RD as detected using continuous cardiorespiratory monitoring (heart rate [HR], oxygen saturation [SpO₂], end-tidal carbon dioxide [etCO₂] and respiratory rate [RR]) on the hospital ward, and will be defined by any one or more of the following:
 - etCO₂ ≤ 15 or ≥ 60 mmHg for ≥3 min OR
 - RR ≤ 5 breaths for ≥3 min OR
 - SpO₂ ≤ 85% for ≥3 min OR
 - Apnea episode lasting >30 s OR
 - Any respiratory Opioid-Related Adverse Event (rORADE)

Secondary outcomes of PRODIGY will include:

1. A comparison of RD risk subjects versus no-risk subjects in terms of:
 - Incidence of adverse events 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 of etCO₂, RR, SpO₂, and the Integrated Pulmonary Index (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.

7. PRODIGY - design

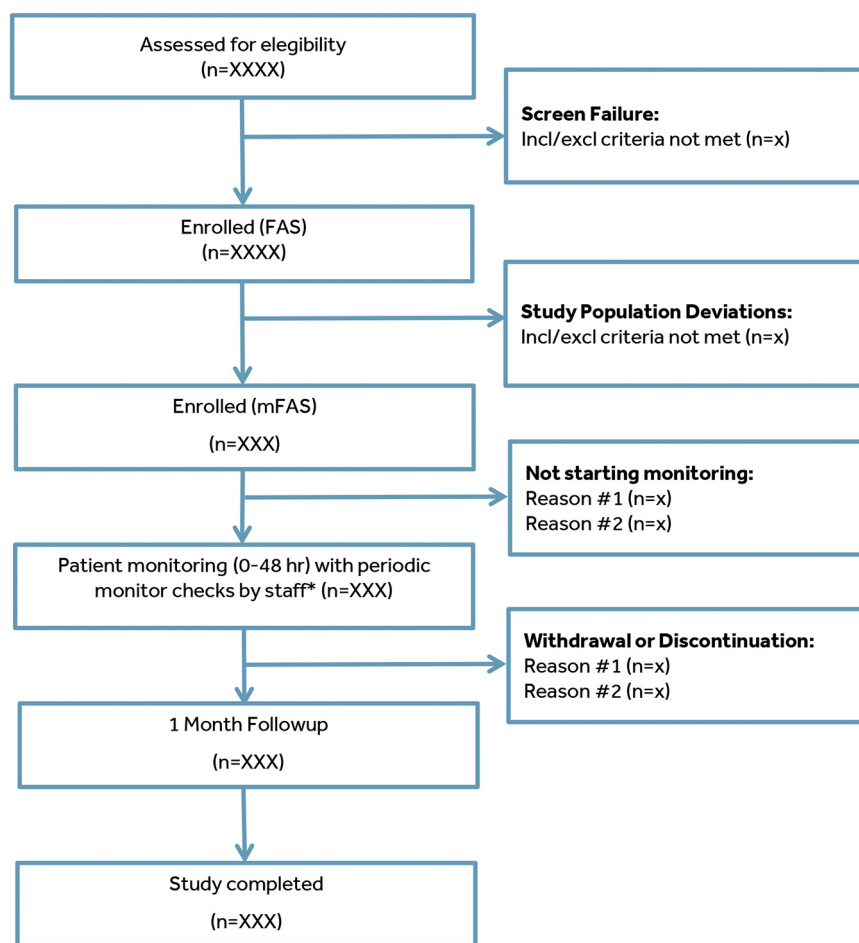
Adult patients receiving parenteral (including epidural) opioid therapy (for post-surgical or non-surgical) pain as the primary analgesic modality on the hospital ward are eligible for the study (Fig. 1). Patients in an “Early recovery after surgery” (ERAS) track and receiving multimodal analgesia are eligible as long as parenteral opioids are the primary analgesic. If the patient is potentially eligible and willing to consider participation, written informed consent is obtained. Exclusion criteria include patients with an expected stay of <24 h, patients receiving intrathecal opioids, American Society of Anesthesiologists (ASA) physical status of V or higher, Do Not Resuscitate (DNR) orders, hospice or receiving end of life therapy, or intubated or mechanically ventilated patients.

Patients will be connected to continuous capnography and oximetry using the Capnostream monitor (Capnostream, Medtronic, Dublin, Ireland) upon arrival on the ward, and monitored for up to a maximum of 48 h. All devices used in this study are commercially available (cleared by United States Food and Drug Administration, Japanese Ministry of Health, Labour, and Welfare Cabinet of Pharmaceuticals and Medical Devices Agency, and European Economic Area (CE marking)) and used within intended use in the participating geographies. The Capnostream™ respiratory monitor provides the ability to continuously monitor etCO₂, respiration rate, heart rate and SpO₂ in patients in nearly any clinical setting. It combines Microstream™ capnography technology and Nellcor™ pulse oximetry technology in an easy to use, portable monitor, designed with features to enhance efficient workflow. The monitor also includes the IPI algorithm, which was developed to help simplify monitoring a patient's complete respiratory status. Integrated Pulmonary Index incorporates via fuzzy logic program four real-time respiratory measurements: end-tidal CO₂ (etCO₂), respiratory rate (RR), pulse oximetry (SpO₂), pulse rate (PR) into a single number. The IPI algorithm number is displayed on a scale from 1 to 10, with 10 indicating a normal respiratory status. This IPI score correlates well with interpretation of respiratory data by experts over a wide variety of clinical situations [50].

The Capnostream monitoring device is light-weight, portable and rugged (Fig. 2A, B) The removable battery pack can run up to 3 h. The device displays end-tidal CO₂ (etCO₂), respiratory rate (RR), pulse oximetry (SpO₂) and pulse rate (PR) along with IPI on an easy to read display screen. However, this screen will be covered for the purposes of the PRODIGY trial, and data will be continuously recorded though not visible for intervention to the healthcare providers at the bedside. Patients will be tethered only with the pulse oximeter skin probe and the nasal cannula (Fig. 3) which serves the dual purpose of a CO₂ sampling line and a conduit to deliver inspired oxygen. The CO₂ sampling line (Fig. 3) is a dual nare sampling line connected to a tubing for oxygen delivery which may be used as an option if a patient needs additional oxygen supplementation. A unique feature of this system is the oral scoop (Fig. 3) that provides accurate sampling for mouth breathers. However, the system will allow for comfort and portability while the patient is ambulating, and this will translate into a better patient experience and compliance with the device.

The Capnostream monitor will only be used in addition to the participating investigation sites' current standard of care for inpatient monitoring. Capnostream data will not be used to influence healthcare interventions, and bedside providers will be blinded to the monitor. All monitor alarms will also be silenced. However, all patients will otherwise be treated according to standard of care including vital sign monitoring per hospital protocol. If the standard of care or hospital policy requires the patient to be continuously monitored with SpO₂, a second SpO₂ device/transducer will be connected to the patient and monitoring will be performed in accordance with local standard practice.

Patient data will be collected using the Remote Data Capture (RDC) management system that allows healthcare providers to enter data directly into the study database via a web interface. Clinical data will be collected throughout the duration of the study from patient screening to the study exit, defined as the one month follow up visit.



*Including 12 hr nocturnal monitoring up to 2 consecutive nights (when possible)

Fig. 1. Study design flow diagram.

Demographics and comorbidities will be collected at enrollment along with previous opioid usage and surgery information. Relevant risk factors for the prediction rule were identified by literature review and include age, sleep-disordered breathing, high risk surgery, previous opioid use and opioid usage during hospitalization, obesity, major organ failure, diabetes, chronic heart failure or other significant cardiac disease, smoking history, and COPD or other significant pulmonary disease [6, 51–55]. Other possible risk factors collected in the case report form can be tested in the prediction rule as well (Appendix A).

Patient safety will be monitored throughout the study and the occurrence of any respiratory adverse events (AE), serious adverse events, or device deficiencies will be documented. Adverse event relatedness to opioid therapy or the device will also be identified. Study site 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.

8. PRODIGY – outcomes

8.1. Primary outcome

Clinical RD will be adjudicated by a Clinical Events Committee (CEC) comprised of a minimum of three non-Medtronic experts experienced in evaluating respiratory compromise, RD, and interpreting continuous monitor data. They will review the monitor data in conjunction with the synchronous clinical data from the patient record to determine episodes of RD, as defined above.

8.2. Sample size

The sample size was calculated using the most appropriate incidences of desaturation, bradypnea, hypoventilation, and apnea available in the literature. The best estimate derived from limited data resulted in an incidence of RD of 12% of patients receiving parenteral opioids. This estimate is primarily driven by the published incidence of oxygen desaturation, since the literature is sparse on the other metrics. 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.

8.2.1. Derivation cohort sample size

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. Enrollment at any single site will be limited to 20% of the total sample size (approximately 330 subjects) to ensure of the data across sites and reduce potential bias.

Simulation studies of prediction models developed using logistic regression have suggested minimum event per variable values of between 5 and 20 for reliable results [56]. An event per variable of 10 is widely advocated as the rule of thumb for multivariable logistic regression analyses. According to this, 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

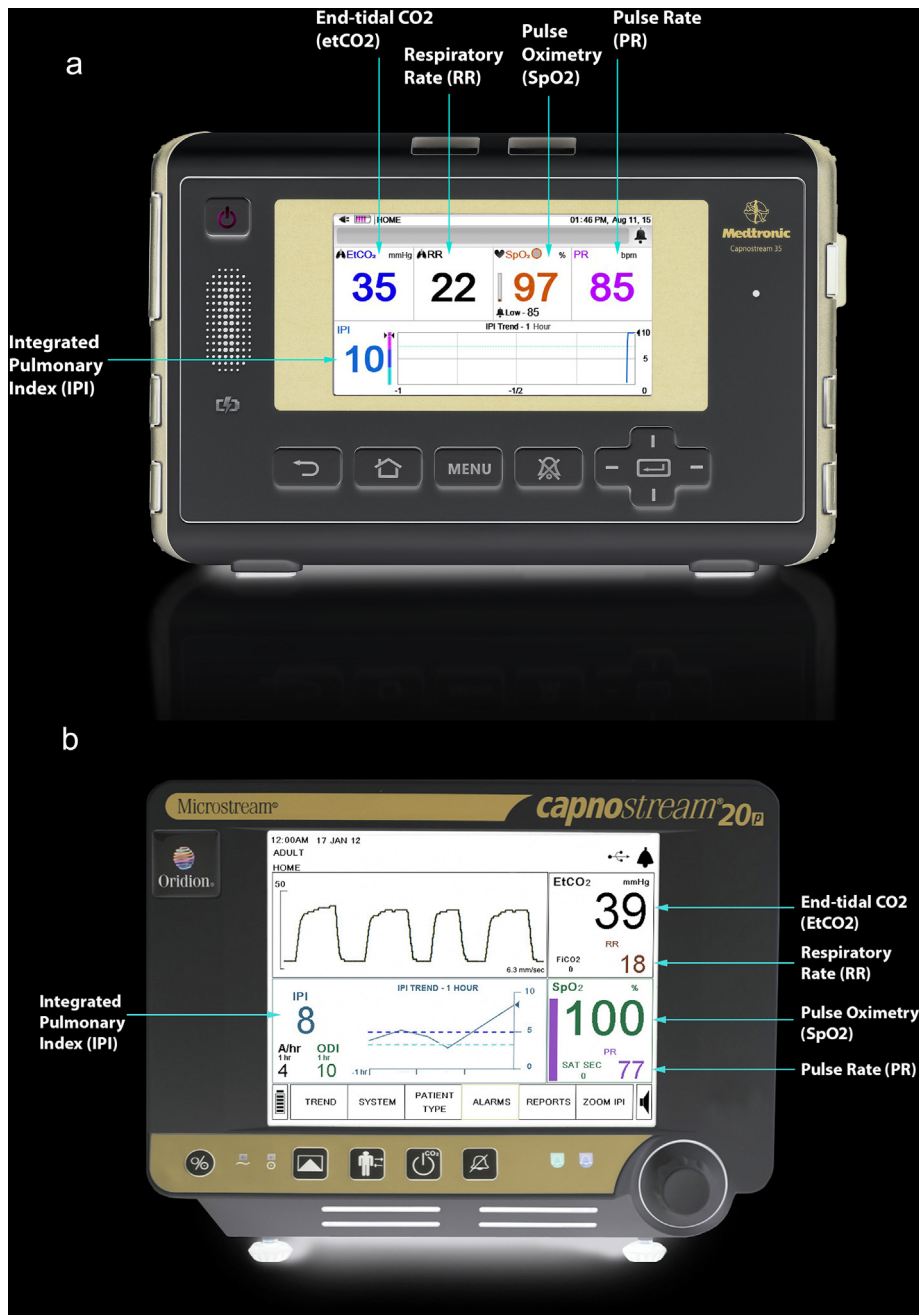


Fig. 2. A: Capnostream™ 35 portable respiratory monitor. ©2017 Medtronic. All rights reserved. Used with the permission of Medtronic. B: Capnostream™ 20_p portable bedside monitor capnograph/pulse oximeter. ©2017 Medtronic. All rights reserved. Used with the permission of Medtronic.

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.

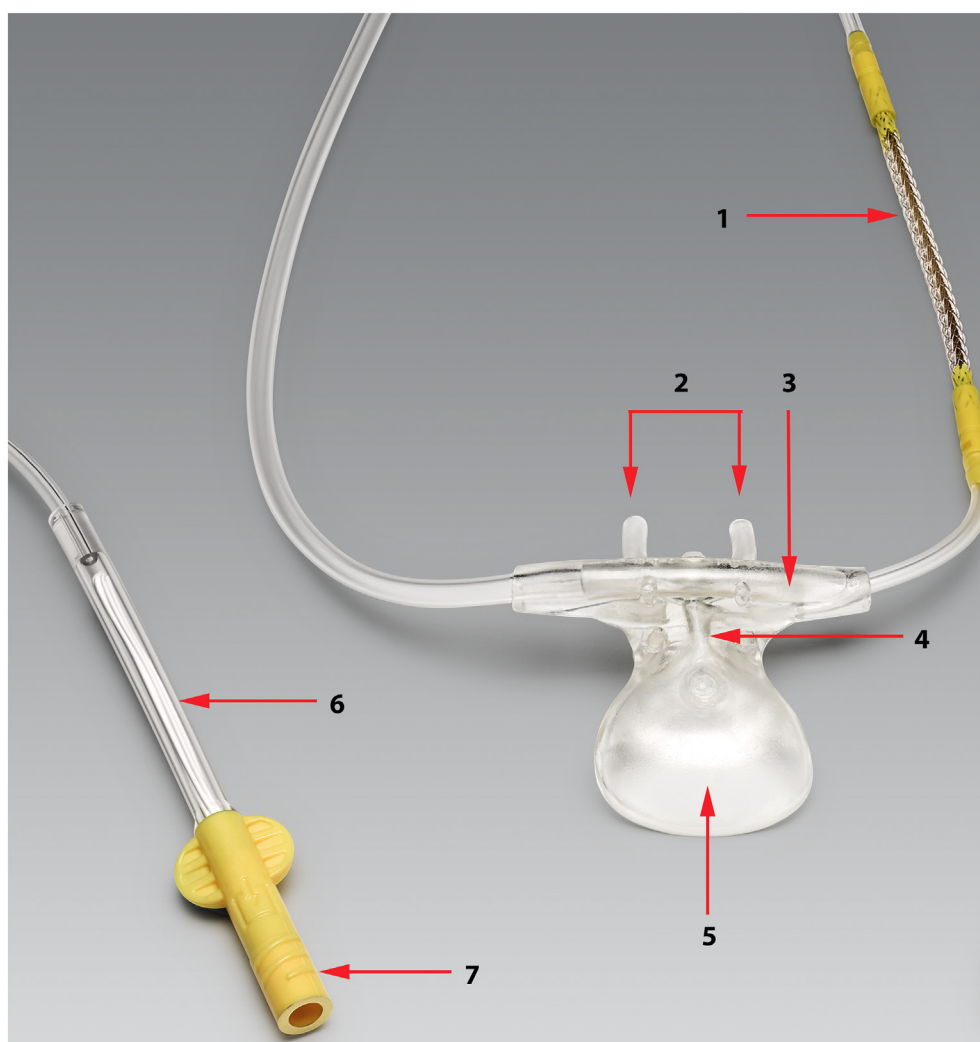
8.2.2. Validation cohort sample size

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 or dropouts the total sample size needed is 1650 subjects.

8.3. Statistical analysis

The full analysis set (FAS) will include all patients enrolled in the study, including those who sign patient informed consent and fulfill

the inclusion and exclusion criteria. The FAS will be used for safety evaluation. The primary analysis will be performed on the modified full analysis set (mFAS), which includes all patients in the FAS starting opioid therapy and monitored on the ward per the protocol. 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. Statistical tests for comparisons of categorical variables will use the Chi-square test or the Fisher exact test, or the Cochran-Mantel-Haenszel test to determine trends for ordinal variables with 3 or more categories, as appropriate. Continuous variable comparisons will be performed using the *t*-test or Wilcoxon test according to the normal or non-normal distribution, respectively.



1. **Nafion® for long term monitoring** (Or alternate moisture reduction technology).
2. **Dual nares sampling** - Designed to ensure proper sampling from either nares.
3. **Tubing for O₂ delivery** (May be used with or without oxygen delivery) - O₂ delivery from holes in front of nasal prongs.
4. **Uni-junction™** - Enables etCO₂ sampling from either the nares or the mouth.
5. **Oral scoop** - Provides accurate sampling for mouth breathers.
6. **0.2 micron Filter** - Sterilizing grade filter designed to reduce risk of biohazard contamination of the monitor.
7. **Connector compatibility** - Connects to all Microstream® enabled products.

Fig. 3. FilterLine® - End-tidal CO₂ sampling line for Microstream™-enabled capnography monitors. ©2017 Medtronic. All rights reserved. Used with the permission of Medtronic.

Rates of adverse events will be computed and reported together with their 95% confidence intervals. Rates will then be compared by either a mixed Poisson model or a negative binomial regression model (if overdispersion is present). Incident rate ratios (IRRs) and 95% confidence intervals will be used to compare the two groups.

The sensitivity and specificity, positive 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 cut-offs in predicting episodes. This analysis will be performed on the set of patients with at least one clinical event. This set of patients, the potential respiratory depression population set (PRDPS) includes all patients in the mFAS and have at least one episode-file and/or clinical event adjudicated. Based on the clinical practice in the opioid use and number of subjects enrolled per center or country, an investigation of center or country effect will be conducted including an

independent variable for center 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 missing data and the type of the imputed variable.

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. A detailed description of methods will be reported in the Statistical Analysis Plan (SAP).

8.3.1. Primary endpoint

The data-splitting method will be used to obtain unbiased internal assessments of accuracy of the statistical model. 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. The derivation

sample will be used for all model development as data transformations, stepwise variable selection, testing interactions, estimating regression coefficients, etc. That model will be defined and applied to the remaining sample for computing calibration measures, c-statistic and clinical usefulness as sensitivity and specificity etc. An alternative approach based on the Bootstrapping for internal validation will be followed if the entire dataset is needed for model development. The bootstrapping will take a large number of samples with replacement from the original sample. The multivariate model will be run for each replication and the performance of each replication will be calculated. The difference between the bootstrapped performance and the model performance will be averaged to obtain an estimation of the “optimism” of the model. The optimism will be used to validate the model.

The logistic regression model will be performed using a backward stepwise selection procedure in which the presence of event will be the dependent variable. For each risk factor, categories and the reference class will be determined. 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 <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 patients will then be stratified using a measure of position (quartiles or deciles) into categories of points that group patients according to the level of risk. Alternatively, the optimal cut off point that maximizes the sensitivity and specificity will be used for stratification. Furthermore, the determination of the estimates of risk associated with each point total will be determined using a logistic regression model. The estimation of risk will be supported by graphical plots and point listing.

9. Conclusion

Patients continue to decompensate on hospital wards. These events add to poor outcomes, activation of rapid response teams, unnecessary admissions to the intensive care units and are a drain on manpower and resources. Available evidence has shown that cardio-respiratory compromise is common, goes undetected and is largely unpredictable. Though continuous monitoring of all patients on the regular floor appears to be the answer, it remains unclear as to who should be monitored with what monitoring parameter. The PRODIGY trial will aid the perioperative physician by developing a validated risk prediction for the prediction of RD for the patient recovering on the hospital ward. Such a tool will be novel and will change clinical practice for hospital systems, anaesthesiologists, intensive care physicians and rapid response teams as they prepare to ensure a safer recovery of post-surgical and medical patients from their illness.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jccr.2018.06.014>.

Funding

The PRODIGY study is funded by Covidien LP. Covidien LP is an indirect, wholly owned subsidiary of Medtronic plc.

Acknowledgement

Formatting support was provided by Mamata Thapa, PhD and Katherine Liu, PhD (Medtronic).

Authors' contributions

All authors qualify for authorship under the ICMJE Recommendations (www.icmje.org), including: substantial contributions to the conception or design of the work (FJO, AKK, CG, PD, and WFB); drafting the article (FJO, AKK); critical revisions of the article (FJO, AKK, CG, PD, and WFB); final approval of the version to be published (FJO, AKK, CG, PD, and WFB).

Conflict of interest

FJO receives scientific advisory board fee from Medtronic. AKK received grant and receives scientific advisory board and consulting fees from Medtronic. CG and PD are employees of Medtronic. WFB receives scientific advisory board fee from Medtronic and Ventinova b.v and received grants from InterReg Wear4health, EU Commission Horizon 2020 STARS, and B. Braun Melsungen.

References

- [1] Sessler DI. Preventing respiratory depression. *Anesthesiology* 2015;122(3):484–5.
- [2] Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK. Perioperative organ injury. *Anesthesiology* 2013;119(6):1474–89.
- [3] 2015 National Healthcare Quality and Disparities Report and 5th Anniversary Update on the National Quality Strategy Content Last Reviewed May 2016. Rockville, MD: Agency for Healthcare Research and Quality; April 2016.
- [4] Cashman JN, Dolin SJ. Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. *Br J Anaesth* 2004;93(2):212–23.
- [5] Perman SM, Stanton E, Soar J, Berg RA, Donnino MW, Mikkelsen ME, et al. Location of in-hospital cardiac arrest in the United States - variability in event rate and outcomes. *J Am Heart Assoc* 2016;5(10) pii: e003638.
- [6] Canet J, Sabaté S, Mazo V, Gallart L, Gama de Abreu M, Belda J, et al. Development and validation of a score to predict postoperative respiratory failure in a multicentre european cohort. A prospective, observational study. *Eur J Anaesthesiol* 2015;32:458–70.
- [7] Felhofer K. Developing a respiratory depression scorecard for capnography monitoring. *Innovations* 2013;4(3, Article 128):1–11.
- [8] Jarzyna D, Jungquist CR, Pasero C, Willens JS, Nisbet A, Oakes L, et al. American society for pain management nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. *Pain Manag Nurs* 2011;12(3):118–45.
- [9] Kessler ER, Shah M, Gurschkus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy* 2013;33(4):383–91.
- [10] Weingarten TN, Herasevich V, McGlinch MC, Beatty NC, Christensen ED, Hannifan SK, et al. Predictors of delayed postoperative respiratory depression assessed from naloxone administration. *Anesth Analg* 2015;121(2):422–9.
- [11] DeVita MA, Smith GB, Adam SK, Adams-Pizarro I, Buist M, Bellomo R, et al. “Identifying the hospitalised patient in crisis” - a consensus conference on the afferent limb of rapid response systems. *Resuscitation* 2010;81:375–82.
- [12] Winters BD, Weaver SJ, Pfoh ER, Yang T, Cuong Pham J, Dy SM. Rapid-response systems as a patient safety strategy: a systematic review. *Ann Intern Med* 2013;158(5 (Part 2)):417–25.
- [13] Sun Z, Sessler DI, Dalton JE, Devereaux P, Shahinyan A, Naylor A, et al. Postoperative hypoxemia is common and persistent: a prospective blinded observational study. *Anesth Analg* 2015;121(3):709–15.
- [14] Khanna AK, Sessler DI, Sun Z, Naylor AJ, You J, Hesler BD, et al. Using the stop-bang questionnaire to predict hypoxaemia in patients recovering from noncardiac surgery: a prospective cohort analysis. *Br J Anaesth* 2016;116(5):632–40.
- [15] Belcher AW, Khanna AK, Leung S, Naylor AJ, Hutcherson MT, Nguyen BM, et al. Long-acting patient-controlled opioids are not associated with more postoperative hypoxemia than short-acting patient-controlled opioids after noncardiac surgery: a cohort analysis. *Anesth Analg* 2016;123(6):1471–9.
- [16] Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology* 2010;112(1):226–38.
- [17] Overdyk FJ, Dowling O, Marino J, Qiu J, Chien H-L, Erslon M, et al. Association of opioids and sedatives with increased risk of in-hospital cardiopulmonary arrest from an administrative database. *PLoS One* 2016;11(2):1–13.
- [18] Lee LA, Caplan RA, Stephens LS, Posner KL, Terman GW, Voepel-Lewis T, et al. Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology* 2015;122(3):659–65.
- [19] Piercy M, Lau S, Loh E, Reid D, Santamaria J, Mackay P. Unplanned admission to the intensive care unit in postoperative patients—an indicator of quality of anaesthetic care? *Anaesth Intensive Care* 2006;34(5):592–8.
- [20] Quinn TD, Gabriel RA, Dutton RP, Urman RD. Analysis of unplanned postoperative admissions to the intensive care unit. *J Intensive Care Med* 2017;32(7):436–43.
- [21] Bhat SASV, Chaudhari LS. Audit of intensive care unit admissions from the operating room. *Indian J Anaesth* 2006;50(3):193–200.
- [22] Sabate S, Mazo V, Canet J. Predicting postoperative pulmonary complications: implications for outcomes and costs. *Curr Opin Anaesthesiol* 2014;27(2):201–9.

- [23] Halpern NA, Pastores SM. Critical care medicine in the United States 2000–2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. *Crit Care Med* 2010; 38(1):65–71.
- [24] Brilli RJ, Spevetz A, Branson RD, Campbell GM, Cohen H, Dasta JF, et al. Critical care delivery in the intensive care unit: defining clinical roles and the best practice model. *Crit Care Med* 2001;29(10):2007–19.
- [25] Halpern NA, Goldman DA, Tan KS, Pastores SM. Trends in critical care beds and use among population groups and Medicare and Medicaid beneficiaries in the United States: 2000–2010. *Crit Care Med* 2016;44(8):1490–9.
- [26] Wagner J, Gabler NB, Ratcliffe SJ, Brown SE, Strom BL, Halpern SD. Outcomes among patients discharged from busy intensive care units. *Ann Intern Med* 2013;159(7):447–55.
- [27] Chrusch CA, Olafson KP, McMillan PM, Roberts DE, Gray PR. High occupancy increases the risk of early death or readmission after transfer from intensive care. *Crit Care Med* 2009;37(10):2753–8.
- [28] Eriksson CO, Stoner RC, Eden KB, Newgard CD, Guise JM. The association between hospital capacity strain and inpatient outcomes in highly developed countries: a systematic review. *J Gen Intern Med* 2017;32(6):686–96.
- [29] Gabler NB, Ratcliffe SJ, Wagner J, Asch DA, Rubenfeld GD, Angus DC, et al. Mortality among patients admitted to strained intensive care units. *Am J Respir Crit Care Med* 2013;188(7):800–6.
- [30] Robert R, Reignier J, Tournoux-Facon C, Boulain T, Lesieur O, Gissot V, et al. Refusal of intensive care unit admission due to a full unit: impact on mortality. *Am J Respir Crit Care Med* 2012;185(10):1081–7.
- [31] Kim SH, Chan CW, Olivares M, Escobar GJ. Association among ICU congestion, ICU admission decision, and patient outcomes. *Crit Care Med* 2016;44(10):1814–21.
- [32] Hung SC, Kung CT, Hung CW, Liu BM, Liu JW, Chew G, et al. Determining delayed admission to intensive care unit for mechanically ventilated patients in the emergency department. *Crit Care* 2014;18(4):485.
- [33] Cardoso LT, Grion CM, Matsuo T, Anami EH, Kauss IA, Seko L, et al. Impact of delayed admission to intensive care units on mortality of critically ill patients: a cohort study. *Crit Care* 2011;15(1):R28.
- [34] Bing-Hua YU. Delayed admission to intensive care unit for critically surgical patients is associated with increased mortality. *Am J Surg* 2014;208(2):268–74.
- [35] Chalfin DB, Trzeciak S, Likourezos A, Baumann BM, Dellinger RP, Group D-Es. Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. *Crit Care Med* 2007;35(6):1477–83.
- [36] Cline SD, Schertz RA, Feucht EC. Expedited admission of patients decreases duration of mechanical ventilation and shortens ICU stay. *Am J Emerg Med* 2009;27(7):843–6.
- [37] Weissman GE, Gabler NB, Brown SE, Halpern SD. Intensive care unit capacity strain and adherence to prophylaxis guidelines. *J Crit Care* 2015;30(6):1303–9.
- [38] Pines JM, Localio AR, Hollander JE, Baxt WG, Lee H, Phillips C, et al. The impact of emergency department crowding measures on time to antibiotics for patients with community-acquired pneumonia. *Ann Emerg Med* 2007;50(5):510–6.
- [39] Pines JM, Hollander JE. Emergency department crowding is associated with poor care for patients with severe pain. *Ann Emerg Med* 2008;51(1):1–5.
- [40] Halpern SD. ICU capacity strain and the quality and allocation of critical care. *Curr Opin Crit Care* 2011;17(6):648–57.
- [41] Morris TA, Gay PC, MacIntyre NR, Hess DR, Hanneman SK, Lamberti JP, et al. Respiratory compromise as a new paradigm for the care of vulnerable hospitalized patients. *Respir Care* 2017;62(4):497–512.
- [42] Hopf HW. Preventing opioid-induced postoperative hypoxemia: no simple answer? *Anesth Analg* 2016;123(6):1356–8.
- [43] Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth R, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013;119(3):507–15.
- [44] Mascha EJ, Yang D, Weiss S, Sessler DI. Intraoperative mean arterial pressure variability and 30-day mortality in patients having noncardiac surgery. *Anesthesiology* 2015;123(1):79–91.
- [45] Vetro J, Natarajan DK, Mercer I, Buckmaster JN, Heland M, Hart GK, et al. Antecedents to cardiac arrests in a hospital equipped with a medical emergency team. *Crit Care Resusc* 2011;13(3):162–6.
- [46] Hillman KM, Bristow PJ, Chey T, Daffurn K, Jacques T, Norman SL, et al. Duration of life-threatening antecedents prior to intensive care admission. *Intensive Care Med* 2002;28:1629–34.
- [47] Schein RMH, Hazday N, Pena M, Ruben BH, Sprung CL. Clinical antecedents to in-hospital cardiopulmonary arrest. *Chest* 1990;98(6):1388–92.
- [48] McGrath SP, Pyke JB, Taenzer AH. Assessment of continuous acoustic respiratory rate monitoring as an addition to a pulse oximetry-based patient surveillance system. *J Clin Monit Comput* 2017;31:561–9.
- [49] Stoelting RK, Overdyk FJ. Essential monitoring strategies to detect clinically significant drug-induced respiratory depression in the postoperative period. Conference on Electronic Monitoring Strategies, Anesthesia Patient Safety Foundation, 8. ; 2011.
- [50] Ronen M, Weissbrod R, Overdyk FJ, Ajizian S. Smart respiratory monitoring: clinical development and validation of the IPI (Integrated Pulmonary Index) algorithm. *J Clin Monit Comput* 2017;31(2):435–42.
- [51] Felhofer K. Developing a respiratory depression scorecard for capnography monitoring. *Inov Pharm* 2013;4(3).
- [52] Jarzyna D, Jungquist CR, Pasero C, Willens JS, Nisbet A, Oakes L, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. *Pain Manag Nurs* 2011;12(3):118–45 e10.
- [53] Kessler ER, Shah M, Gruschkus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy* 2013;33(4):383–91.
- [54] Weingarten TN, Herasevich V, Mcglinch MC, Beatty NC, Christensen ED, Hannifan SK, et al. Predictors of delayed postoperative respiratory depression assessed from naloxone administration. *Anesth Analg* 2015;121(2):422–9.
- [55] Safe use of opioids in hospitals. *Sentin Event Alert*, 49. ; 2012. p. 1–5.
- [56] Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49(12):1373–9.