Supplemental Table 1. PRODIGY Trial Sites.

Region	Trial Site
United States	University of Colorado Hospital
	Emory University Hospital
	Brigham and Women's Hospital
	Beaumont Hospital
	Buffalo General Medical Center
	MetroHealth Medical Center
	Cleveland Clinic
	The Ohio State University Wexner Medical Center
	Providence Regional Medical Center
Europe	Hôpital Foch (France)
	University Hospital Bonn (Germany)
	Maastricht University Medical Center (Netherlands)
	Hospital Clinico Universitario de Valencia (Spain)
Asia	Okayama University Hospital (Japan)
	Jikei University School of Medicine Hospital (Japan)
	National University Hospital (Singapore)

Supplemental Table 2. Detailed PRODIGY Trial Inclusion and Exclusion Criteria.

Inclusion Criteria[a]	Exclusion Criteria
Patient was age ≥18, 20, or 21 years in United States/Europe, Japan, and Singapore, respectively	Patient whose hospital stay was expected to be ≤24 h
Patient was able to give informed consent	Patient received intrathecal opioids
Receiving parenteral opioid therapy for post-surgical or non-surgical pain on hospital general care floor	Post-surgical patient with American Society of Anesthesiologist (ASA) physical status V or higher
	Patient with status of Do Not Resuscitate (DNR)
	Patient receiving hospice or end of life therapy
	Patient was ventilated or intubated
	Patient was unwilling or unable to comply with trial procedures
	Patient was a member of a vulnerable population (per ISO 14155)
	Patient participating in another potentially confounding drug or device clinical trial

[a]Patients on oxygen and/or positive airway pressure were eligible for enrollment

Supplemental Table 3. Definitions of Clinical Episodes and Events.

Term	Definition
Respiratory Depression	Any of the following: respiratory rate ≤5 bpm for ≥3 minutes; SpO_2 ≤85% for ≥3 minutes; $ETCO_2$ ≤15 or ≥60 mmHg for ≥3 minutes; apnea episode lasting >30 seconds; or any respiratory opioid-related adverse drug event
Opioid-related adverse drug event	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs considered to be solely due to the use of opioid medication. Opioid-related adverse drug events were measured using standard of care bedside monitoring, including best clinical judgement of the bedside nurse/clinician.
Respiratory opioid-related adverse drug event	Any opioid-related adverse drug event involving impaired respiratory function. Respiratory opioid-related adverse drug events were measured using standard of care bedside monitoring, including best clinical judgement of the bedside nurse/clinician. Anticipated respiratory opioid-related adverse drug events included but were not limited to:
	Narcotic overdose that required 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 require invasive mechanical ventilation
	Upper airway obstruction requiring airway support measures (oral or nasal)
	Respiratory insufficiency or failure requiring transfer to the ICU
	Cardiopulmonary arrest
	Death due to respiratory or pulmonary related complications

Abbreviations: bpm = breaths per minute; SpO_2 = oxygen saturation; $ETCO_2$ = end-tidal carbon dioxide; NMBA = neuromuscular blocking agent; ICU = intensive care unit

Supplemental Table 4. Prioritization of Potential Respiratory Depression Episode Adjudication by the Clinical Event Committee, Based on the Clinical Importance of the Episode.

Priority Level	Definition
1	**Any clinical event, independent of potential respiratory depression episode from continuous monitoring**. If multiple clinical events occurred for 1 patient, events were adjudicated in chronological order.
2	**Multiple episodes of ≥2 continuous monitoring parameters (SpO_2, $ETCO_2$, respiratory rate, apnea)**. If a patient had multiple Priority 2 instances, the data files with the highest number of potential episodes was reviewed first.
3	**Multiple episodes of the same continuous monitoring parameter (SpO_2, $ETCO_2$, respiratory rate, apnea)**. If a patient had multiple Priority 3 instances, the data files were reviewed in order based on the type of episode: SpO_2, $ETCO_2$, respiratory rate, apnea.
4	**Any overnight episodes of the same continuous monitoring parameter (SpO_2, $ETCO_2$, respiratory rate, apnea)**. If a patient had multiple Priority 4 instances, the data files were reviewed in order based on the type of episode: SpO_2, $ETCO_2$, respiratory rate, apnea.

For each patient, episodes of the earliest time occurrence were adjudicated first within each priority level. All clinical events were adjudicated, and all level 2, 3, and 4 priority episodes were adjudicated such that after the first confirmed respiratory depression episode was identified for each patient, subsequent potential respiratory depression episodes were not adjudicated. To ensure interrater reliability, at least 3 clinical event committee members separately reviewed each of the 5,768 potential respiratory depression episodes evaluated. All clinical event committee members were non-Medtronic, non-trial investigator clinicians with experience evaluating respiratory depression and interpreting continuous monitoring data. Final respiratory depression episode adjudication was determined by the majority agreement of individual clinical event committee members. Average 2 by 2 agreement, weighted for the number of adjudications, was 82% between clinical event committee members, suggesting strong agreement between these perioperative respiratory medicine experts. During adjudication, the clinical event committee had access to clinical data (including duration and time periods of opioid use) and Capnostream™ 20p or 35 portable bedside monitor parameters but was blinded to all other patient information.

Abbreviations: SpO_2 = oxygen saturation; $ETCO_2$= end-tidal carbon dioxide

Supplemental Table 5. Variables Included and Excluded in Univariable and Multivariable Analysis of Respiratory Depression.

N	Predictors	Reason for Inclusion/Exclusion
31	Age[a], Sex, BMI[a], Current Smoker[a], Acute Bronchitis, Aortic Aneurysm, Aortic Valve Disease[a], Asthma, Cerebral Aneurysm, Chronic Bronchitis, CHF[a], COPD[a], Coronary Artery Disease[a], Diabetes Type I[a], Diabetes Type II[a], Hypertension, Kidney Failure[a], Liver Failure[a], Mitral Valve Disease[a], Myocardial Infarction[a], Sleep Disorders[a] (known or suspected sleep disorders, including OSA), Peripheral Vascular Disease, Pulmonary Hypertension, Sepsis, Stroke, Transient Ischemic Attack, Number of Different Opioids, Opioid Naïve, High Risk Surgery[a], Open Surgery, Duration of Surgery	Included: Both bivariable and final model analysis[b]
1	Multiple opioid or concurrent central nervous system sedating medication[a]	Excluded: >90% prevalence
9	Chronic Restrictive Lung Disease, Cystic Fibrosis, Emphysema, Multi Organ Dysfunction Syndrome[a], Muscular Dystrophy, Orthostatic Hypotension, Pulmonary Fibrosis, Sarcoidosis, Amyotrophic Lateral Sclerosis	Excluded: <0.5% prevalence[c]
3	ASA Physical Status, Neck Circumference, Pneumonia	Excluded: >25% correlation[d]
2	Surgical Patient, Intravenous and Epidural Opioid Route[a]	Excluded: Other reasons[e]

[a]Predictor described in the literature as a risk factor for respiratory depression[1-6]
[b]Geography and Effective length of monitoring quartiles were included as random effects.
[c]Covariables with very low prevalence (<0.5%) were excluded from the multivariable model.
[d]From the correlation analysis some covariables correlated with other covariables were excluded using statistical (correlation significant cut off >0.25) and clinical judgement. ASA score was excluded but several factors contributing to ASA score, such as BMI, CHF, and sleep disorders, were used in model derivation. Neck circumference was strongly correlated with BMI which is a standard clinical parameter. Thus, neck circumference was excluded. Pneumonia was excluded because it was strongly correlated with COPD, which is a reported risk factor for respiratory depression.
[e]Medical patients were enrolled only in United States; opioid route and doses may be used in future ad hoc analysis
Abbreviations: ASA = American Society of Anesthesiologists; BMI = body mass index; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disorder; OSA = Obstructive Sleep Apnea

Online-Only References

1. Canet J, Sabate S, Mazo V, 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(7):458-470.
2. Felhofer K. Developing a Respiratory Depression Scorecard for Capnography Monitoring. *Inov Pharm.* 2013;4(3).
3. Jarzyna D, Jungquist CR, Pasero C, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. *Pain Manag Nurs.* 2011;12(3):118-145 e110.
4. 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):383-391.
5. Weingarten TN, Herasevich V, McGlinch MC, et al. Predictors of Delayed Postoperative Respiratory Depression Assessed from Naloxone Administration. *Anesth Analg.* 2015;121(2):422-429.
6. Safe use of opioids in hospitals. *Sentin Event Alert.* 2012(49):1-5.

Supplemental Table 6. Frequency of Variable Selection During Model Validation.

Variable	Frequency of selection[a] during bootstrapping (500 replicates)	Frequency of selection[a] during cross-validation (50 replicates)
Age classes (yr)	**88.8%**	**96%**
Sex (Male)	**88.6%**	**96%**
BMI (kg/m^2)	11.2%	0%
Current Smoker	8.2%	16%
Length of Surgery (h)	14.2%	8%
Opioid Naive	**23.6%**	**34%**
Number of Distinct Opioids	6.2%	2%
Cardiac Disorders		
Aortic Aneurysm	2.4%	0%
Aortic Valve Disease	2.8%	0%
Chronic Heart Failure	**30.8%**	**46%**
Coronary Artery Disease	3.8%	2%
Hypertension	41%	66%
Mitral Valve Disease	5.6%	8%
Myocardial Infarction	2%	0%
Pulmonary Hypertension	6.4%	8%
Hepatobiliary Disorders		
Liver Failure	3.2%	0%
Infections		
Sepsis	4.6%	0%
Metabolism and Nutrition Disorders		
Diabetes - Type I	7.2%	4%
Diabetes - Type II	4.2%	0%
Musculoskeletal and Connective Tissue Disorders		
Kidney Failure	12.8%	10%
Respiratory, Thoracic and Mediastinal Disorders		
Acute Bronchitis	12.2%	2%
Asthma	15%	12%
Chronic Bronchitis	3.2%	2%
Chronic Obstructive Pulmonary Disease	7.4%	2%
Sleep Disorders	**37.4%**	**68%**
Vascular Disorders		
Cerebral Aneurysm	7.6%	6%
Peripheral Vascular Disease	1.6%	0%
Stroke	1.8%	0%
Transient Ischemic Attack	11.6%	8%

[a]The multivariable logistic regression models used stepwise selection with entry 0.25, stay criteria 0.15, and respiratory depression as the dependent variable.

Supplemental Table 7. Adverse Events in the Modified Full Analysis Set (N=1,335).

Adverse Event	Total Patients (N = 1335)
Number of Adverse Event NE (NP, Y%)	367 (313, 23.4%)
Cardiac disorders	8 (8, 0.6%)
Congenital, familial and genetic disorders	1 (1, 0.1%)
Ear and labyrinth disorders	2 (2, 0.1%)
Gastrointestinal disorders	26 (25, 1.9%)
General disorders	166 (163, 12.2%)
Hepatobiliary disorders	2 (2, 0.1%)
Infections and infestations	48 (45, 3.4%)
Injury, poisoning, and procedural complications	22 (21, 1.6%)
Investigations	6 (6, 0.4%)
Metabolism and nutrition disorders	3 (3, 0.2%)
Musculoskeletal and connective tissue disorders	4 (4, 0.3%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (3, 0.2%)
Nervous system disorders	9 (9, 0.7%)
Product issues	4 (4, 0.3%)
Psychiatric disorders	2 (2, 0.1%)
Renal and urinary disorders	4 (4, 0.3%)
Respiratory, thoracic, and mediastinal disorders	47 (44, 3.3%)
Skin and subcutaneous tissue disorders	5 (4, 0.3%)
Surgical and medical procedures	2 (2, 0.1%)
Vascular disorders	3 (3, 0.2%)

Adverse event: Any untoward medical occurrence, unintended disease or injury, or untoward clinical sign, observed by standard of care patient monitoring. All adverse events were recorded independent of their relationship to opioids or respiratory depression.
Abbreviations: NE= Number of events; NP = Number of patients

Supplemental Table 8. Opioid-related Adverse Events, Detection by Continuous Monitoring, and PRODIGY Scores for Patients with Opioid-related Adverse Events. Twenty-two opioid-related adverse events occurred during the trial period, of which eleven occurred outside of continuous capnography and pulse oximetry monitoring. Adverse events occurring outside of continuous monitoring were excluded from model derivation.

Type of Opioid-related Adverse Event	Opioid-related Adverse Events (N)	Adverse Events Detected by Continuous Monitoring[a,b]	PRODIGY Score[c]		
			High Risk (≥15 points) (N)	Intermediate Risk (≥8 & <15 points) (N)	Low Risk (<8 points) (N)
Hypoxia	13 (12)	6	9	1	2
Respiratory Failure	3 (3)	0	0	3	0
Bradypnea	1 (1)	1	0	0	1
Hypotension	1 (1)	1	0	1	0
Discomfort	2 (2)	1	0	1	0
Somnolence	1 (1)	1	N/A	N/A	N/A
Abdominal Pain	1 (1)	0	N/A	N/A	N/A
Sum	22 (18)[c]	10[a,b]	9	6	3

[a]Four adverse events (2 hypoxia, 1 respiratory failure, 1 discomfort) took place before capnography and pulse oximetry monitoring commenced

[b]Seven adverse events (4 hypoxia, 2 respiratory failure, 1 abdominal pain) took place after capnography and pulse oximetry monitoring ended

[c]Four patients each had 2 opioid-related adverse events; PRODIGY score was determined once per patient. One opioid-related adverse drug event (hypoxia) occurred during continuous monitoring but was not detected.

Supplemental Table 9. Adverse Event Incidence and Action Taken for Patients With and Without ≥1 Respiratory Depression Episode (Full Analysis Set = 1,495).

Endpoint	Any Adverse Event		Adverse Event with Any Action		Adverse Event with Hospitalization[a]		Adverse Event with Surgical Procedure		Adverse Event with Opioid Administration		Adverse Event with Rescue Action	
Respiratory Depression Episodes	**No Episodes**	**≥ 1 Episode**	**No Episodes**	**≥ 1 Episode**	**No Episodes**	**≥ 1 Episode**	**No Episodes**	**≥ 1 Episode**	**No Episodes**	**≥ 1 Episode**	**No Episodes**	**≥ 1 Episode**
Patients (N)	840	655	840	655	840	655	840	655	840	655	840	655
Patients with Event (N)	212	139	79	84	49	47	24	21	72	68	16	29
Events (N)	237	175	85	100	51	53	26	22	83	81	17	33
Patients with Event (%)	25.2	21.2	9.4	12.8	5.8	7.2	2.9	3.2	8.6	10.4	1.9	4.4
Cumulative Exposure Time (Days)[b]	21387	17499	25133	19128	26074	20184	26395	20619	25115	19378	26544	20279
Rate (Pt/Day)	0.011	0.01	0.003	0.005	0.002	0.003	0.001	0.001	0.003	0.004	0.001	0.002
95% CI	0.010-0.013	0.009-0.012	0.003-0.004	0.004-0.006	0.001-0.003	0.002-0.003	0.001-0.001	0.001-0.002	0.003-0.004	0.003-0.005	0.000-0.001	0.001-0.002
Incidence Ratio	0.902		1.546		1.364		1.083		1.249		2.464	
95% CI	0.686-1.188		1.171-2.041		1.014-1.777		0.791-1.483		0.931-1.676		1.734-3.501	
Significance (p value)	0.464		0.002		0.040		0.618		0.138		<0.001	

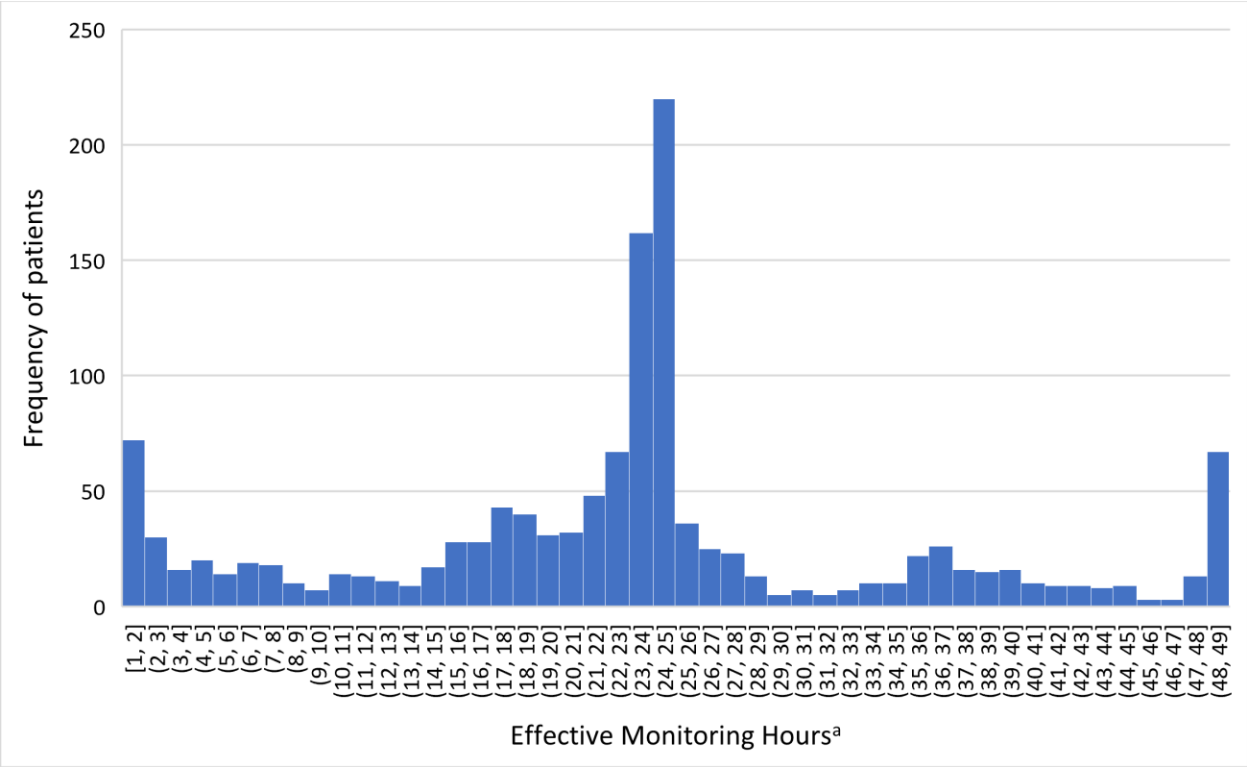
[a]Hospitalization defined as prolongation of initial hospital stay or re-hospitalization during ≤30 day follow-up

[b]Cumulative exposure time is the sum of the individual exposure time per patient.

Supplemental Table 10. Healthcare Resource Utilization, Including Hospital Length of Stay and ≤30 Day Readmission of Patients with and without Respiratory Depression.

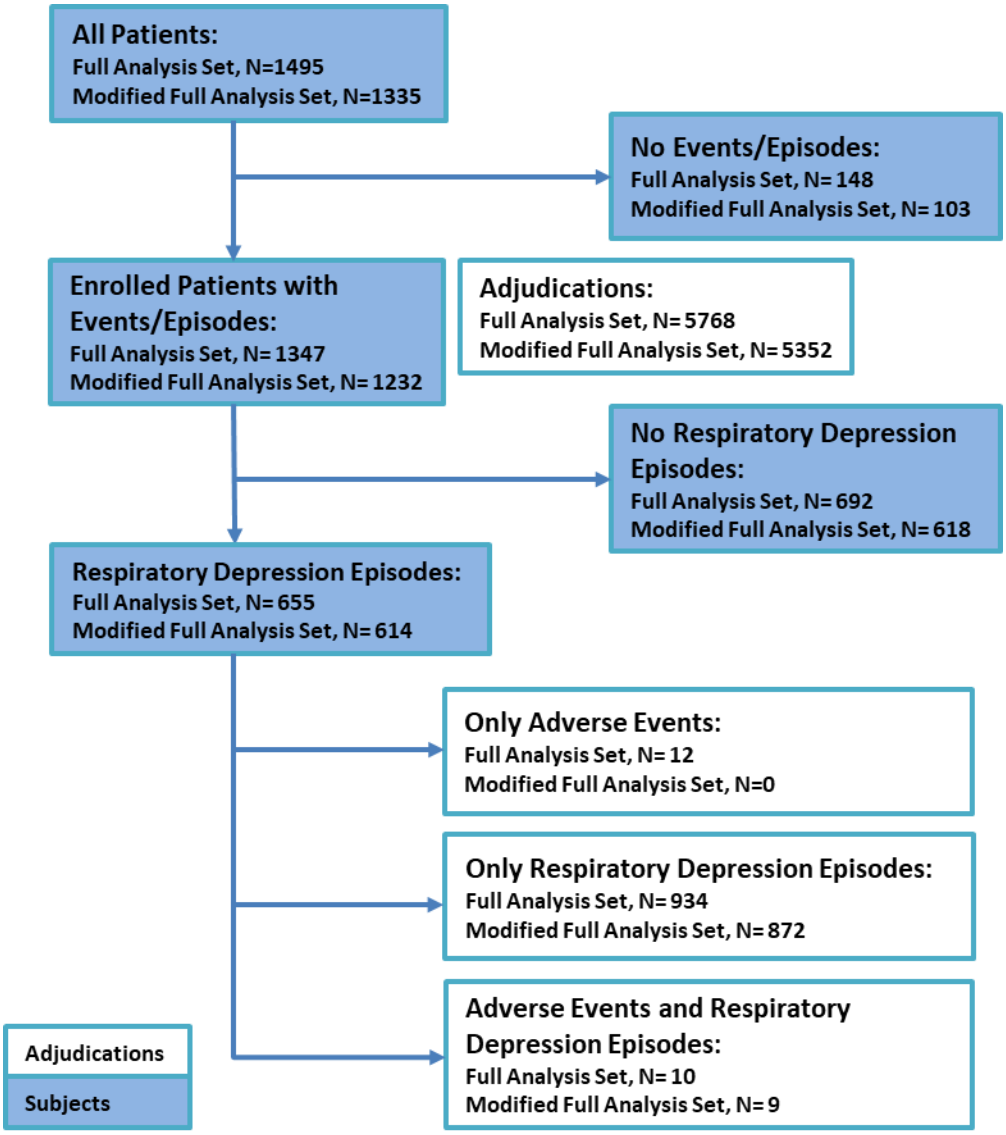
Patient Characteristic	Patients with ≥ 1 Respiratory Depression Episode	Patients without Respiratory Depression	Significance (p value)
Mean Length of Stay (N Days, SD) [N Patients]	10.5 (10.8) [614]	7.7 (7.8) [721]	<0.0001
Percent patients with ≤30 day readmission (N/Pts)	4.1% (23/556)	4.0% (24/597)	0.92
Primary Diagnosis at Readmission	**Patients (N, %) with ≥ 1 Respiratory Depression Episode (N = 23)**	**Patients (N, %) without Respiratory Depression (N = 24)**	
Blood and lymphatic system disorders	0 (0%)	1 (4.17%)	
Gastrointestinal disorders	5 (21.74%)	4 (16.67%)	
General disorders	2 (8.7%)	1 (4.17%)	
Infections and infestations	5 (21.74%)	5 (20.83%)	
Injury, poisoning and procedural complications	1 (4.35%)	2 (8.33%)	
Investigations	0 (0%)	1 (4.17%)	
Metabolism and nutrition disorders	1 (4.35%)	0 (0%)	
Musculoskeletal and connective tissue disorders	3 (13.04%)	1 (4.17%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.35%)	0 (0%)	
Nervous system disorders	2 (8.7%)	0 (0%)	
Product issues	0 (0%)	1 (4.17%)	
Respiratory, thoracic and mediastinal disorders	1 (4.35%)	2 (8.33%)	
Surgical and medical procedures	2 (8.7%)	6 (25%)	
Vascular disorders	1 (4.35%)	1 (4.17%)	
Missing	1 (4.35%)	0 (0%)	

Supplemental Figure 1. Distribution of Effective Continuous Capnography and Pulse Oximetry Monitoring Time in Patients who Started Monitoring (N=1,335). Effective continuous monitoring was determined by subtracting any time in which the patient was temporarily disconnected from monitoring equipment from the total monitoring time (h).



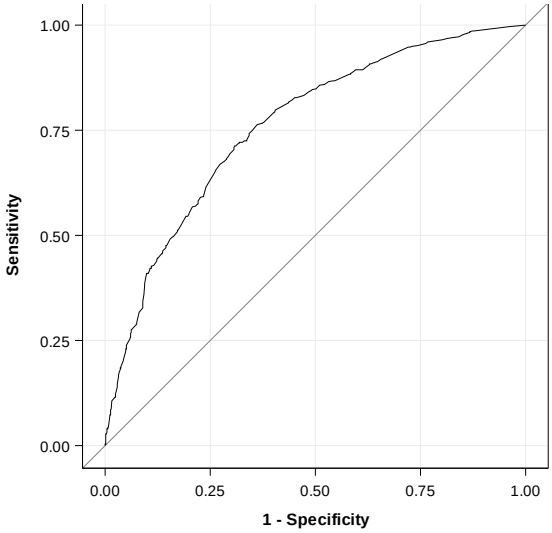
[a]The extreme categories “1” and “49” contain data between 0.002 and 1 hour and data between 48 and 110.3 hours, respectively.

Supplemental Figure 2. Clinical Event Committee Adjudication Flow Diagram. The clinical event committee adjudicated potential respiratory depression episodes detected by continuous capnography and pulse oximetry in all enrolled patients. Differences between all enrolled patients (Full Analysis Set) and enrolled patients who received opioids and started monitoring (Modified Full Analysis Set) are highlighted for each adjudication step, including incidence of adverse events with and without respiratory depression episodes.

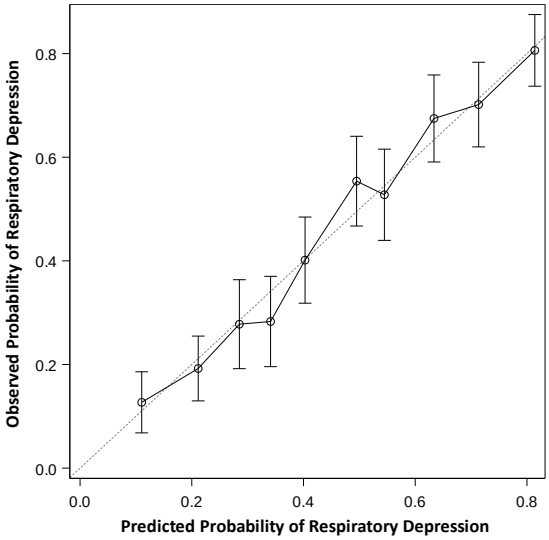


Supplemental Figure 3. Assessment of Multivariable Risk Prediction Model Accuracy. (A) Receiver operating characteristic curve of multivariable risk prediction model, with an area under the curve equal to 0.7606. This represents the relationship between sensitivity and specificity and indicates the probability that the multivariable model will correctly distinguish patients with respiratory depression from those without respiratory depression. (B) Calibration plot of multivariable risk prediction model, comparing the predicted vs observed probability of respiratory depression, used to assess the prediction accuracy of the model. Patients were divided into deciles of the predicted probability of the fitted logistic model, and within each group, the mean predicted probability was calculated. Error bars represent 95% confidence intervals.

A.

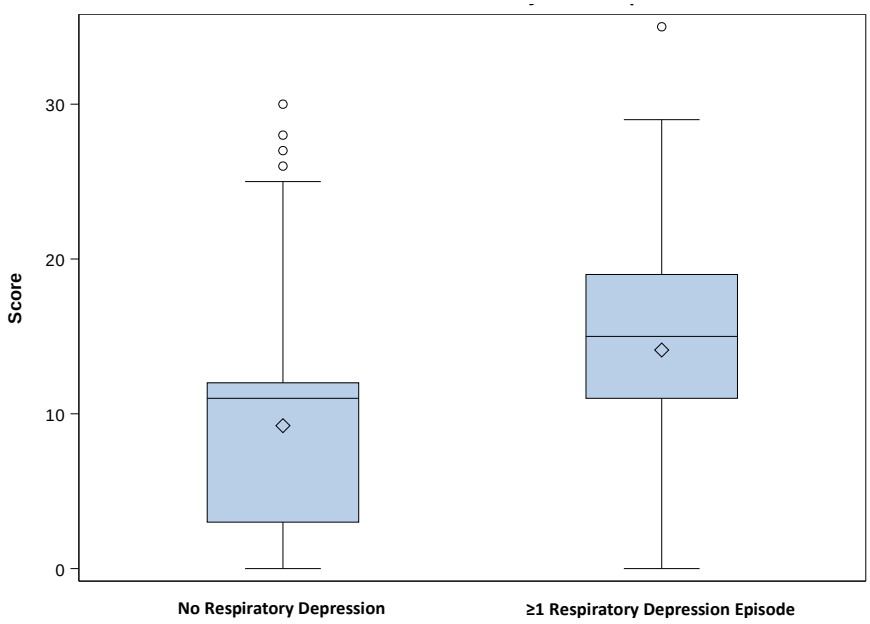


B.



Supplemental Figure 4. PRODIGY Score Distribution (A) by Respiratory Depression Occurrence and (B) by Risk Score Class, including comparison of the expected probability of respiratory depression and the observed frequency of patients with respiratory depression.

A.



B.