Continuous Ward Monitoring with the GE Portrait Mobile Monitoring Solution: the COSMOS trial

A pilot study

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Version 16

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Background

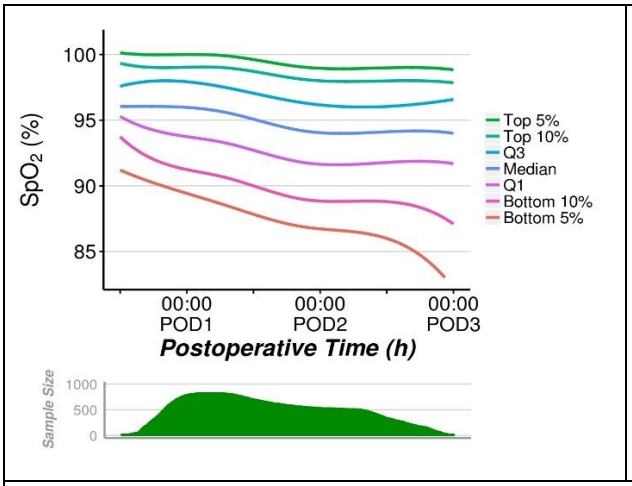
When patients having major surgery reach the post-anaesthesia care unit, families naturally assume that they have survived the most dangerous part of the perioperative experience. Their assumption is wrong. Mortality in the 30 days after surgery is more than 100 times higher than intraoperative mortality.[1,2] In fact, if the month after surgery were considered a disease, it would be the third leading cause of death in the United States.[3]

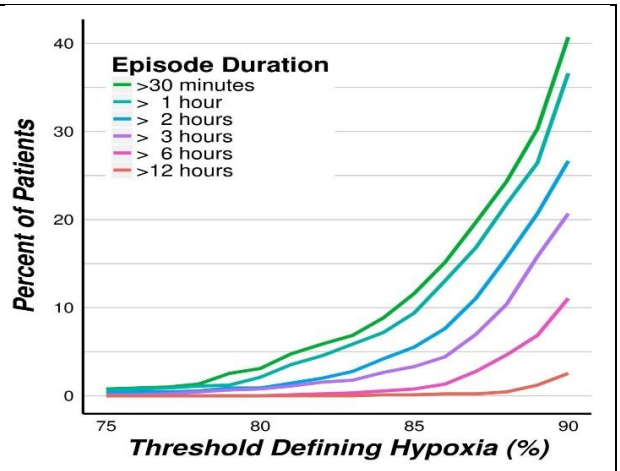
Most 30-day postoperative mortality occurs during the initial hospitalization, that is, under direct medical care in our highest-level facilities. The most common causes of 30-day postoperative mortality are major bleeding which cannot easily be prevented, and cardiopulmonary complications which possibly can be.[4] Respiratory complications are also common — and are of special interest because nearly all are preventable.

Ward respiratory compromise

The reported incidence of ward respiratory compromise is 0.3% to 3.4% when defined by interventions such as naloxone administration,[3,6,7] but is 21% when defined by prolonged oxygen desaturation and 41% when defined by bradypnea episodes.[6,8]

We quantified hypoxemia on the surgical wards using blinded continuous saturation monitoring (n=833). Postoperative hypoxemia was common, serious, and prolonged (**Fig. 1**). For example, 20% of patients demonstrated an average of 10 minutes of saturation <90% *per hour over their entire hospitalization* (**Fig. 2**). And soberingly, 90% of serious hypoxemic episodes (saturation <90% for ≥1 full hour) were completely missed by nurses conducting routine vital sign monitoring at four-hour intervals.[5]

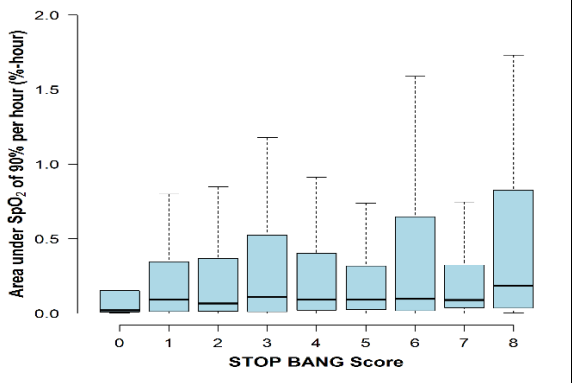




Figs. 1 and 2. Continuous *blinded* saturation monitoring in 850 patients recovering from non-cardiac surgery. The figure on the left shows that by the second postoperative day, more than 10% of all saturation measurements were <905. The figure on the right shows that desaturation was common, profound, and prolonged. For example, 10% of patients had a continuous hour of saturation ≤85%. Nursing vital sign monitoring at 4-hour intervals missed more than 90% of these episodes.[5]

We recently finished PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY), a prospective, observational study of continuous capnography and oximetry conducted in the United States, Europe, and Asia.[6] Monitor alerts and data were blinded. Respiratory compromise episodes were defined by respiratory rate ≤5 bpm for ≥3 minutes; oxygen saturation ≤85% for ≥3 minutes; end-tidal carbon dioxide ≤15 or ≥60 mmHg for ≥3 minutes; apnea episode lasting >30 seconds; or any respiratory Opioid-Related Adverse Events (rORADE). One or more respiratory compromise episodes were detected in 615 (46%) of 1,336 patients over the initial 24 postoperative hours.

Various risk factors for developing respiratory depression have been reported for post-surgical patients including sleep apnea, obesity, snoring, old age, post-surgery, increased opioid dose requirement, concomitant use of other sedating medications, comorbidities like preexisting pulmonary or cardiac disease, use o patient-controlled opioid analgesia, and smoking.[1,4,7,16,17] Nonetheless, postoperative respiratory events remain difficult to predict. For example, we have shown that STOP-BANG scores (a measure of obstructive sleep apnea risk) are not associated with the amount of postoperative oxygen desaturation (**Fig. 3**).[7] Similarly, risk was not reduced by using short-acting opioids in patient controlled analgesia systems (**Fig. 4**).[8]



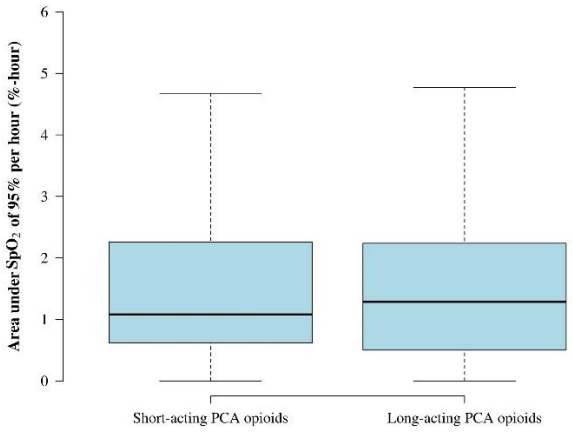


Fig. 3 (left). STOP-BANG scores (a measure of obstructive sleep apnea risk) are not associated with the amount of postoperative oxygen desaturation.[7] **Fig. 4 (right)**. Hypoxemia risk was not reduced by using short-acting opioids in patient-controlled analgesia systems.[8]

In PRODIGY there was some relationship between baseline and procedural characteristics, but respiratory events could not be reliably predicted, with area under the receiver-operating characteristics curve of only 0.7. Available information thus indicates that it is difficult to reliably predict which postoperative inpatients will desaturate, or the severity of their hypoxemia. *A corollary is that all patients need to be continuously monitored to reliably detect respiratory compromise early enough to intervene effectively and presumably prevent serious complications*.

The role of opioids

Opioid analgesia remains the primary pharmacologic intervention for managing pain in hospitalized patients.[19] However, up to 80% of patients who received opioid analgesics experience Opioid-Related Adverse Drug Events (ORADEs).[4] The Joint Commission on Hospital Accreditation identifies improper patient monitoring as one of the main causes of ORADEs.[1,5]

Opioid-induced respiratory depression is traditionally defined using surrogate measures, such as hypoventilation with or without oxygen desaturation, and is often a diagnosis of exclusion[10] and is probably much under-estimated.[11,12] Opioid-related adverse events, including respiratory depression, are associated with increased length of stay (mean five additional days), readmission (15.8% vs 9.4% in patients without events), and cost (mean increase $10,000).[13]

Preventing respiratory complications

The general care floor is a low acuity inpatient environment. However, nearly half of all in-hospital cardiorespiratory events occur on the general care floor, often with catastrophic outcomes.[14,15] A national registry identified 44,551 acute respiratory events in United States hospitals, with an associated in-hospital mortality of nearly 40%.[15] Early recognition of respiratory compromise through continuous respiratory monitoring on the general care floor has been advocated to reduce morbidity and mortality.[16,17]

Respiratory compromise precedes respiratory depression, respiratory failure, and death. Early interventions probably prevent or mitigate decompensation[10]. Detection of a patient's respiratory compromise status before progression can help avert unwarranted outcomes and the possible need for critical care. Despite this, there are no universally accepted guidelines to direct effective and safe assessment and monitoring practices for postoperative patients.

The earliest warning of respiratory failure may be subtle changes in vital signs 6-8 hours before critical cardiac and respiratory decompensation ensues.[18] Intermittent ward monitoring often misses these early patterns or infers incorrect patterns, which are key to preventing catastrophic events. For example, vital sign monitoring at 4-hour intervals misses >90% episodes of prolonged hypoxemia.[11] Similarly, in a closed claims analysis of the American Society of Anesthesiologists, most of more than 357 opioid-related respiratory events were deemed preventable with adequate monitoring and timely responses.[19] Because most postoperative respiratory compromise is due to opioids, it is difficult to predict which patients will have respiratory events.[8]

Pulse oximetry alone can lead to inaccurate assessment of patients' condition, especially when supplemental oxygen is needed: the Anesthesia Patient Safety Foundation recommended the use of continuous electronic monitoring of oxygenation *and ventilation* for all patients given postoperative opioids.[11]

Taenzer and colleagues evaluated continuous ward saturation monitoring with pager notification to nurses. They reported that continuous monitoring reduced emergent rescue events (median [95% CI]) from 3.4 [2, 5] to 1.2 [0, 5] per 1,000 patients and reduced ICU transfers from 5 [4, 7] to 3 [1, 4] per 1,000 patients.[20] However, the before-and-after design is subject to time-dependent confounding, regression to the mean, and the Hawthorne effect.[21,22] Ochroch and colleagues conducted a randomized trial of continuous ward saturation monitoring (n=1,219), but did not find that monitoring resulted in a reduction in ICU transfers (6.7% monitoring versus 8.5% control).[23] We note that ICU transfer may not be the optimal outcome since continuous monitoring might detect patients who would benefit from ICU care earlier than otherwise, and that initiating ICU care early could reduce serious complications such as myocardial injury or respiratory disasters. Despite their limitations, both studies suggest that continuous saturation monitoring may be helpful.

Beyond "failure to rescue"

Ward monitoring has hardly changed over last half-century, although there have been major changes in hospital populations. Substantive changes include: 1) ambulatory surgery is routine for relatively healthy patients, with 60% of all surgery in the United States now done on an out-patient basis; 2) it is now common to perform large operations in elderly and frail patients; and, 3) even when patients are admitted after surgery, the duration of hospitalization is usually short. Ward patients are therefore much sicker now than previously.

In a series of studies, we have shown that conventional intermittent ward vital sign monitoring misses most hypoxemia, hypotension, and hypertension. Furthermore, we cannot reliably predict which patients will develop respiratory complications or when they will occur. Continuous ward monitoring is therefore the only approach likely to identify instability before it becomes critical or even irreversible.

Cardiopulmonary 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.[24,25] As might thus be expected, it is well established that vital signs deteriorate 6–12 hours before cardiac and respiratory arrests occur[26-28] — which is the basis for having hospital rapid-response teams which undoubtedly save lives.[29] The difficulty is that rapid response teams largely prevent further damage *after* patients experience critical events; patients would be better served if we could detect deterioration early and therefore *prevent* critical episodes.

Life-threatening ward complications including cardiocirculatory and respiratory failure are usually preceded by abnormalities in vital signs that occur minutes to hours earlier.[30,31] Recognition of even subtle changes in basic vital signs may allow clinical deterioration to be identified well before serious adverse events occur. Continuous vital sign monitoring may therefore prompt clinical interventions that prevent complications, or at least moderate their severity.

There are already battery-powered, untethered ward systems that continuously monitor a combination of physiologic variables, such as blood pressure, electrocardiogram, heart rate, oxygen saturation, respiratory rate, body position, activity, and location.[32,33] New biosensor material and digital developments will allow further miniaturization of measurement systems, and non-invasive continuous measurement of other physiological variables.[34] Continuous monitoring is likely to facilitate rapid detection of abnormalities and trigger clinical interventions.[29]

Silber and colleagues reported in 1992 that critical events occurred at comparable rates in hospitals with good and poor outcomes,[35] an observation that has subsequently been confirmed.[36] This led to the concept of "failure to rescue," the theory being that the best hospitals intervened earlier and more effectively than others, thus improving outcomes.

The difficulty, of course, is that "failure to rescue" applies *after* patients experience a critical event. Far better would be to *prevent* critical events. Or to put this another way, we need to move beyond failure to rescue, and instead intervene *before* critical events – rather than trying to pick up the pieces afterwards. Continuous ward monitoring and the associated data handling systems may well allow clinicians to intervene before critical events — thereby potentially saving lives.[37-40]

We plan a pilot study to evaluate patient tolerance of the GE Portrait Mobile Monitoring Solution, along with appropriate alert thresholds, and clinical utility. The system is a novel battery-powered untethered monitor for continuous monitoring of oxygen saturation, respiratory rate, and pulse rate that is designed for use by patients on surgical wards. The initial phase will evaluate patient tolerance, with clinicians and patients blinded to monitor data. Results will be used to evaluate the frequency of respiratory events and pulse rate abnormalities. These data will be used to design clinical alert settings, based on various durations at various thresholds (e.g., saturation <85% for >1 minute). Our main goal will be to identify clinically meaningful vital sign abnormalities with a minimum of false alerts. Secondarily, we will evaluate the frequency and duration of abnormalities, and the fraction that are detected clinically.

In the second phase of the pilot, clinicians will be unblinded to the GE Portrait monitors, and alerts provided based on the durations and threshold identified in the initial part of the pilot. The primary outcomes will be clinician tolerance and the extent to which clinicians believe that vital sign trending and alerts provided useful information rather than distraction. Specifically, we will assess the fraction of alerts that clinicians deemed meaningful, and the fraction that resulted in clinical interventions. In the third phase of the pilot, the durations and thresholds for saturation, respiratory rate, and pulse rate that trigger alerts will be adjusted based on results from the second phase.

Data obtained in the proposed pilot cohort will guide design of a future robust randomized trial comparing clinical interventions and serious complications with blinded versus unblinded continuous ward monitoring.

Specific Aims

Initial phase

The general goals of the initial phase are to collect initial data to evaluate the frequency and nature of vital sign abnormalities, individually and as a composite, while also socializing the Portrait monitor with clinicians. Blinded data collected in this phase will be recorded for subsequent analysis and used to design alarm thresholds that will identify clinically meaningful events with few "false alarms." The tentative goal will be an average of several alerts per day per monitored patient. Clinicians will be completely blinded during this phase.

Primary Aim. Collect blinded data to evaluate the frequency and duration of vital sign abnormalities detected by the GE Portrait monitor, and the fraction that are detected clinically and the extent to which they overlap.

Secondary Aim 1. Design clinically meaningful alerts based on the data collected and abnormalities detected while avoiding false alerts.

Secondary Aim 2. Determine the frequency of the alerts, using criteria determined in Aim 1.

Secondary Aim 3. Determine the fraction of potentially serious vital sign abnormalities detected by GE Portrait monitoring that are also detected by clinicians using routine every four-hour monitoring and vice versa.

Second phase

In the second phase, patients will be randomized to blinded or unblinded GE Portrait monitoring. We will determine whether unblinded monitoring reduces the cumulative duration of vital sign abnormalities. We will also assess the extent to which clinicians find alerts to be useful versus distracting.

Primary Aim. Determine whether patients with unblinded continuous ward monitoring with the GE Portrait Mobile Monitoring Solution experience less time with vital sign abnormalities as defined in the initial phase of the study. Specifically, we will test the primary hypothesis that the cumulative duration of vital sign abnormalities (using criteria determined in Phase 1) is shorter with unblinded than blinded GE Portrait monitoring in patients recovering from major noncardiac surgery.

Secondary Aim. Evaluate the extent to which clinicians believe that alerts from the GE Portrait monitor are clinically meaningful.

Third phase

In this phase, we will refine the alert thresholds developed Phase 1 if necessary. Again, we will estimate the extent to which unblinded monitoring reduces the cumulative duration

of vital sign abnormalities. And on an exploratory basis, we will determine whether unblinded monitoring reduces a composite of interventions for vital sign abnormalities. These results will provide guidance for a future full trial with "hard" outcomes.

Primary Aim. Determine whether unblinded continuous ward monitoring with the GE Portrait Mobile Monitoring Solution reduces vital sign abnormalities. Specifically, we will test the primary hypothesis that the cumulative duration of vital sign abnormalities (using criteria refined in Phase 2) is shorter with unblinded than blinded GE Portrait monitoring in patients recovering from major noncardiac surgery.

Exploratory Aim 1. Determine whether continuous ward saturation, ventilation, and pulse rate monitoring reduces a collapsed composite of substantive respiratory interventions. Components of the composite will be:

- Naloxone administration;
- Insertion of oral or nasal airways;
- Non-invasive ventilatory support including for bag and mask ventilation;
- Rapid Response Team activation;
- Unplanned ICU transfer;
- Unplanned intubation;
- CPR;
- Death.

Methods

We anticipate enrolling patients cared for in 2-4 designated surgical wards at the Cleveland Clinic Main Campus. The study will be restricted to designated wards because active nursing engagement and training will be required. Ward assignments are largely determined by bed availability and therefore cannot be reliably predicted preoperatively. Consent will therefore be obtained shortly after patients are admitted to one of the participating wards. A screening log will be maintained.

There will be no restriction on sex, race, or ethnicity; all qualifying patients will be asked to consider the study. Our prospective cohort study will be conducted with all necessary regulatory approvals and will be registered on ClinicalTrials.gov. A full statistical analysis plan will be developed before any data are evaluated. Reporting will be consistent with the CONSORT guidelines. The project will be managed by a Steering Committee consisting of study leaders who are not involved in day-to-day enrollment and data acquisition.

We plan to enroll between 100 patients in the first phase, 150 patients in the second phase, and 250 in the third phase. We expect that patient enrollment for each will last between 2 and 4 months. Data analysis for each phase and consideration of thresholds will likely require several months between phases 1 and 2, and between

phases 2 and 3. Data cleaning and analysis for phase 3 will require at least several months.

Subject selection

Consenting patients will be **eligible** if they:

1. Are admitted to one of the wards equipped with the GE Portrait Mobile Monitoring Solution;
2. Are ≥18 years old;
3. Are designated American Society of Anesthesiologists physical status 1-4;
4. Had major noncardiac surgery lasting at least 1.5 hours;
5. Are expected to remain hospitalized at least two postoperative nights;
6. Had general anesthesia with or without neuraxial anesthesia.

Patients will be **ineligible** if they:

1. Have language, vision, or hearing impairments that may compromise continuous monitoring;
2. Are designated Do Not Resuscitate, hospice, or receiving end of life care;
3. Have previously participated in the study.
4. Patients who have “Implantable Minute Ventilation Rate Responsive Pacemakers”

Protocol

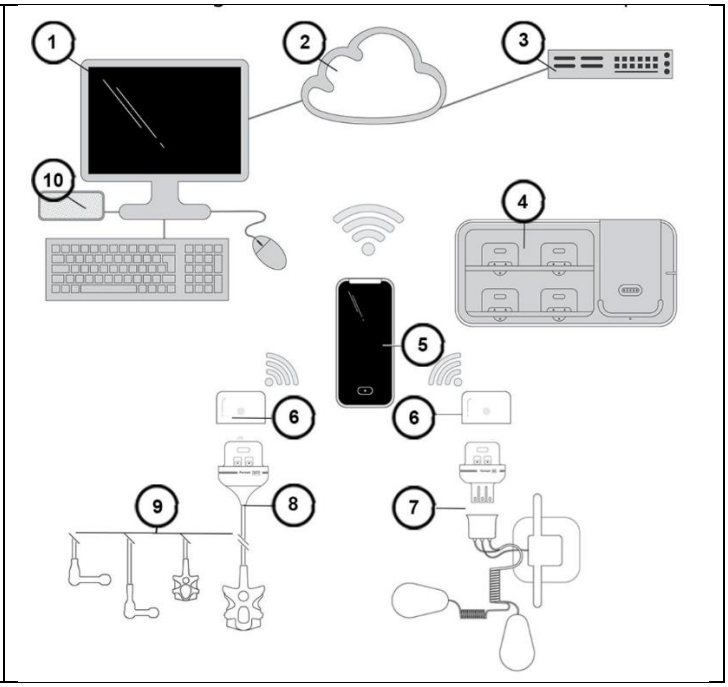
In all cases, good judgement will predominate. Clinicians should always act in their patients’ best interests, irrespective of this protocol.

Patients will be enrolled postoperatively after admission to a surgical ward. Consequently, anesthetic management will not be controlled. Postoperative analgesia will be entirely at clinical discretion and can include field, plane, and nerve blocks. No aspect of clinical care is prescribed by this protocol.

All patients will have normal vital sign assessments by nurses at 4-hour intervals per Cleveland Clinic routine, and more often as clinically indicated. Clinicians may make any interventions they believe necessary. *Thus, no patients will be denied routine monitoring and management.* Participating patients will have continuous pulse oximetry, ventilation, and heart rate monitoring *in addition to all routine vital signs* as tolerated for 72 postoperative hours using the GE Portrait ward monitoring solution (Fig. 5, Appendix 1). Clinicians will be carefully trained not to rely on measurements from the GE Portrait, and to always confirm concerning values with conventional monitors and physical assessment. Details of network communication are provided in Appendix 2.

Fig. 5. Patient connections for the GE Portrait Mobile Monitoring Solution continuous ward saturation, ventilation, and heart rate system.

1. Computer
2. Monitoring network
3. Core services software
4. Charger
5. Hub
6. Sensor batteries
7. Respiration sensor
8. Saturation sensor
9. Second saturation sensor
10. Alert unit



The patient units are powered by small rechargeable batteries that last at least 24 hours. Investigators will swap depleted batteries for fully charged ones daily. Data from the patient module will be transmitted to a small hub in each patient's room using MBAN (similar to Bluetooth) proprietary secure communication. The hub normally rests in a charging dock, and can be taken with patients if they care to leave their rooms. The hub retransmits monitor data in real time via the hospital's secure "internal" Wi-Fi system to display screens in clinical areas and to the Department of Outcomes Research, which is a double-locked card-key controlled location restricted to Departmental investigators.

During the initial phase of the study, all monitoring will be clinician-blinded. That is, recorded for *post hoc* analysis. During the subsequent phases of the study, patients will be randomly assigned to unblinded versus blinded monitoring. In both cases, information from the GE Portrait Monitor will be recorded, but will be available to clinicians only when patients are assigned to unblinded monitoring. Randomization will be based on computer-generated codes, in random blocks of 4-8 patients, without stratification. A web-based system will be accessed by investigators after consent is obtained. Allocation will therefore be concealed as long as practical.

Measurements

Baseline demographic and morphometric characteristics will be recorded, including height, weight, and sex. Elements of the STOP-BANG sleep apnea questionnaire will be recorded.[7,41,42] Cardiopulmonary risks will be recorded, including hypertension requiring treatment, diabetes requiring oral medications or insulin, history of previous myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, current smoking status, and pack-years of smoking history. Cardiovascular and pulmonary medications will be similarly recorded by category, including beta blockers,

angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, statins, bronchodilators, and inhaled steroids.

Baseline laboratory values (within 30 days before surgery) will be recorded on an as-available basis, including albumin, BNP, NT-ProBNP, troponin, and FEV1. Results of sleep studies will be recorded.

Anesthesia will be characterized as general, neuraxial, or combined. Use of peripheral plane and nerve blocks will also be recorded. Routine anesthetic variables will be recorded including time-weighted average volatile anesthetic partial pressure, fluid type and volume, estimated blood loss, and transfusions. Postoperative opioids will be converted to morphine sulphate equivalents (Appendix 3).[43] On an as-available basis, we will record hemoglobin and troponin concentrations obtained during the initial four postoperative days.

Outcome definitions

Initial phase

Primary Aim. As in previous studies,[5,44] we will present vital sign abnormalities as continuous functions of duration and severity of vital sign abnormalities. An advantage of this approach is that we do not need to pre-define thresholds and will instead present various combinations of durations and thresholds for bradycardia, tachycardia, saturation, and respiratory rate. See Figure 2 as an example for saturation.

However, to evaluate clinical detection of vital sign abnormalities we need to define thresholds. We will consider the following thresholds and continuous durations to be clinically meaningful: A) saturation <90% for 30 minutes; B) heart rate >110 beats/min for 30 minutes; C heart rate <40 beats/min for 15 minutes; D) respiratory rate <6/minute for 30 minutes or <3/minute for 10 minutes; and, E) respiratory rate >20 for 30 minutes. Because physiological signals are inherently noisy, all values will be electronically smoothed to some degree, but raw data summaries will be used as a cross-check (see Data Analysis for details).

Secondary Aim 2. Continuous ward monitoring with the GE Portrait Mobile Monitoring Solution detects a composite of vital sign abnormalities more often than routine nursing vital signs at 4-hour intervals in noncardiac surgical patients over the initial 72 postoperative hours in the surgical ward while hospitalized. Components of the composite will be: A) saturation <85% for ≥60 seconds,[5] B) pulse rate >130 beats/min for 30 secs,[45] C) pulse rate <40 beats/min for 30 secs,[46] D) low respiratory rate <4/minute for 30 secs E) high respiratory rate >25 for 120 secs, and, F) apnea >120 secs.

Phases 2 and 3

An investigator will ask the relevant clinician (usually a nurse) to rate each alert as clinically meaningful or not. Specifically, clinicians will be asked to rate alerts as “critical,” “important,” “informative,” or “false or distracting.” The terms will intentionally not be further defined, thereby allowing caregivers to determine themselves the extent to which

a given alert was helpful or not. Caregivers will be queried in person shortly after each alert, typically within 15 minutes. The thresholds, determined in the initial phase, will be set to generate an average of about 2 alerts per patient per day — and therefore will not be onerous for clinicians.

We will also evaluate the following interventions in our composite: 1) drugs that slow or speed heart rate; 2) administration of bronchodilators; 3) initiating or increasing oxygen administration (increment in oxygen concentration, flow rate, or administration mode); 4) mask, CPAP or high-flow oxygen (e.g., 60 L/min) respiratory support; 5) nursing requests for physician evaluation; 6) activation of a Rapid Response Team; 7) intubation; 8) cardiopulmonary arrest; and, 8) transfer to a monitored ward or critical care unit. Investigators, in consultation with clinicians, will determine which interventions were made, and whether they were prompted by GE Portrait alerts.

Data management

Study data will be entered into a custom secure Redcap database that will be maintained on secure Cleveland Clinic servers and backed up to remote sites nightly. The system will record who accessed the randomization system and when it was accessed. The database will include appropriate logic and range checks, and track all changes.

Most data will be obtained directly from the GE Portrait monitor and electronic records. Other values will be entered manually directly entered into Redcap from source documents or initially recorded on case report forms for subsequent transfer to Redcap.

Data analysis

Pulse oximetry data are difficult to analyze due to the high degree of variability in saturation that occurs within each patient. We will thus use an approach similar to our previous analysis.[5] On one hand, patients might experience frequent, short episodes of more severe hypoxemia, while on the other hand, average SpO_2 may linger within slightly abnormal or dangerous territory for hours. The latter is difficult to ascertain from the raw SpO_2 data. We will therefore consider both raw and smoothed (or filtered) SpO_2 data.

For the raw data, we will conduct two analyses: **First,** to assess the overall exposure to hypoxemia for each patient, we will summarize the distribution of number of hypoxic minutes per hour of monitoring using incidence curves. Various thresholds defining hypoxemia will be used to generate the incidence curves. **Second,** we will use quantile regression[47] to characterize the median, quartiles, 10^{th} and 90^{th} percentiles, and 5^{th} and 95^{th} percentiles of the distribution of SpO_2 across patients as a function of postoperative time. Nonlinearities in these quantile curves will be taken into account by incorporating restricted cubic splines for the time variable in the quantile regression models.

For the analyses of filtered SpO_2 data, we will smooth each individual patient's SpO_2-versus-time profile using a Gaussian kernel smoother (i.e., the smoothed estimate of SpO_2 for a specific time point will be a weighted average of the surrounding SpO_2

values, where the weights will be determined according to a Gaussian distribution centered at that time point with an inter-quartile range of 3 hours). Using the smoothed profiles, we will then estimate the incidence of hypoxic episodes of varying duration under a range of SpO_2 thresholds characterizing hypoxemia.

Phase I

Primary Aim. Collect blinded data to evaluate the frequency and duration of vital sign abnormalities detected by the GE Portrait monitor, the fraction that are detected clinically, and the overlap between them. We will use descriptive statistics such as median [quartiles] and mean (SD) to summarize clinical detection of vital sign abnormalities using the definitions given in Outcome Definitions using both the raw data and also using the data smoothing techniques described above. Raw data summaries will be helpful so that truly extreme values are not routinely "smoothed away" in the algorithms described in Data Analysis.

Secondary Aim 1. We will design clinically meaningful alerts based on the data collected and abnormalities detected, while avoiding false alerts. This will involve estimating sensitivity and specificity for detecting true abnormalities across the range of possible alert cut-points and choosing cut-points which maximize both sensitivity and specificity. Accuracy, along with positive and negative predictive values, will be reported. All estimates will be reported with confidence intervals.

Secondary Aim 2. We will determine the optimal frequency of the alerts, using criteria determined in Secondary Aim 1. This will be largely descriptive, but will involve a tradeoff between increasing the frequency of alerts and the corresponding loss to sensitivity and specificity.

Secondary Aim 3. We will estimate the proportion and corresponding confidence interval of potentially serious vital sign abnormalities detected by GE Portrait monitoring that are also detected by clinicians using routine every four-hour monitoring, and vice versa.

Phase II

Primary Aim. We will assess the treatment effect of unblinded continuous ward monitoring versus blinded monitoring on the cumulative duration of the various vital sign abnormalities using parametric (e.g., s-sample t-test) or non-parametric (e.g., Wilcoxon-Mann-Whitney test), as appropriate.

Secondary Aim. In the unblinded group we will evaluate the fraction of alerts from the GE Portrait monitor that clinicians designate dichotomously as clinically meaningful. Results will be presented as a percentage with 95% confidence intervals.

Phase III

Primary Aim. We will test whether and estimate the extent to which unblinded continuous ward monitoring with the GE Portrait Mobile Monitoring Solution reduces the time with

vital sign abnormalities as defined in the initial phase of the study using statistical methods similar to those described in the primary aim for Phase II above.

Exploratory Aim 1. We will assess whether and the extent to which unblinded continuous ward monitoring of saturation, ventilation, and pulse rate monitoring reduces a collapsed composite of substantive respiratory interventions as described in specific aims using a Chi-Square test and estimating the relative risk and its confidence interval. As a secondary analysis we will assess the treatment effect using a distinct effects generalized estimating equation (GEE) model which estimates a separate treatment effect for each component and then averages them (average relative effect method, ARE).[48] [49] This method prevents components with higher frequency, which also may be less severe, from driving the treatment effect results. It simultaneously accounts for the correlation across components, and allows assessment of the treatment-by-component interaction. Finally, we will estimate the common effect (or "global") treatment effect across the components in a GE model estimating a single effect.

Sample Size Considerations

We plan for 100 patients in the first phase, 150 in phase 2, and 250 in phase 3. When comparing groups on continuous outcomes for Phases 1, 2 and 3, respectively, we will have 90% power at the 0.05 significance level to detect a difference in means of 0.66, 0.53 and 0.41. When comparing groups on binary outcomes such as the collapsed composite outcome in Phase III we will have 90% power at the 0.05 significance level to detect relative risks of 0.10, 0.30 or 0.45 or stronger given corresponding control group incidences of 0.10, 0.20 or 0.30.

Limitations

Active participation and engagement from ward clinicians will be essential, including nurses, hospitalists, anesthesiologist members of the acute pain team, and surgeons. To that end, key personnel from each specialty are co-investigators and have agreed to champion the project, including the Associate Chief Nursing Officer for Nursing Research and a senior member of a relevant surgical department. Thus, while considerable effort will be required, we anticipate high engagement from participating clinicians.

Our experience with four other continuous ward monitoring systems is that most patients tolerate monitoring well, but there are inevitably patients who drop out of monitoring studies. And even for those who remain in a study, there are often gaps of varying duration. Our experience is that paying patients, even a trivial amount, much improves cooperation with monitoring. The GE Portrait system is untethered and small, and therefore should be relatively well tolerated.

Clinical interventions are multifactorial and usually based on many factors. It will thus not always be possible to reliably attribute a particular intervention to a GE Portrait alert. Nonetheless, by personally asking clinicians in real time, we will reasonably be able

to estimate whether the GE Portrait alert was the initial prompt for further evaluation and eventual treatment.

Human Subjects Protection

In all cases, good judgement will predominate. Clinicians should always act in their patients' best interests, irrespective of this protocol.

The study will be conducted with IRB approval and written patient consent. The study will be restricted to designated wards because active nursing engagement and training will be required. Furthermore, the GE monitoring system will only be available in selected wards.

The study will be guided by a Steering Committee that will review enrollment, protocol compliance, data quality, and adverse events. Safety will be evaluated after each pilot phase, and more often if deemed necessary.

Patients will be paid $1/hour of successful monitoring time, to a maximum of 72 postoperative hours. Our intent is to pay patients for monitoring time, even if unsuccessful because of technical difficulties, but not for periods when they electively remove or disable the monitors. Payment will be made by check about 8 weeks after discharge.

The GE Portrait ward monitoring system is not yet FDA cleared. We thus request a non-significant-risk device exemption from the IRB. The basis for our request is:

1) The device itself is battery powered, external, and presumably inherently risk-free. Detailed documentation of design and process control, and electrical safety is provided in Appendix 1;
2) Clinical staff will never make clinical decision based on values from the GE Portrait monitor. Any potential abnormalities will be confirmed with convention monitors and clinical examinations. To the extent that alerts are unfounded, they will disrupt nurses but not harm patients. Based on the initial blinded portion of the proposed pilot, alert thresholds will be designed to occur no more often than an average of twice per day per patient.
3) True alerts (confirmed with conventional monitors) will potentially improve care by allowing clinicians to intervene and perhaps prevent serious cardiorespiratory complications.
4) Continuous monitoring data will be transmitted with a secure proprietary communication algorithm (similar to Bluetooth) to a hub in patient rooms, and from there to the Clinic's internal secure Wi-Fi system. Connections to the Clinic's data system will be made with full approval from the responsible HIPAA data security team. Ward monitoring data will thus be as secure as other clinical data.

The major risk to patients will be discomfort from wearing the GE Portrait Mobile Monitoring Solution. However, the level of discomfort will be slight since the system consists of a small light-weight battery powered unit and several "stick-on" pads. Of

course, patients will always have the prerogative to remove the system themselves should it become burdensome.

Nurses will be key participants in the study, and their responses to alerts are important outcomes. (We consider them to be co-investigators.) Specifically, they will have the option to respond to alerts from the GE Portrait system, and their responses will be recorded. We will also ask them to rate the utility of the alerts. Specific alerts thresholds will be based on the results of the initial phase of the study and will be designed to not exceed an average of 2 alerts per patient per day. Use of the monitors will thus minimally disturb nurses even if all alerts are considered distractions — which seems highly unlikely. No record of nurse identification will be kept. That is, nurse responses will be completely unlinked to individuals.

Data will be analyzed by statisticians in the Department of Outcomes Research and resulting manuscripts will be written by investigators. De-identified data will be shared with GE at the end of study for future research, product development, and marketing purposes.

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Appendix 1

Design and safety specifications for the GE continuous ward monitoring system.

Appendix 2

Details of network connection and data handling.

Appendix 3

Opioid conversions[43]

Drug	***Route***	***Dose***
Morphine	IV	10 mg
Fentanyl	IV	100 µg
Fentanyl	100 µg patch	100 µg
Hydrocodone	PO	30 mg
Hydromorphone	IV	1.5 mg
Hydromorphone	PO	7 mg
Meperidine	IV	75 mg
Oxycodone	PO	20 mg
Oxycodone/ Acetaminophen 5/325	PO	6 tabs
Hydrocodone/ Acetaminophen 5/500	PO	6 tabs
Tramadol	PO	150 mg
Propoxyphene/ Acetaminophen 130	PO	1 tab

IV = intravenous, PO = oral.