Postoperative Consequences of Intraoperative NOL Titration

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Background

Opioid requirements in hospitalized patients varies at least ten-fold depending on a host of factors, many of which are unknown to clinicians or poorly characterized in medical records. Important factors include genetic sensitivity, alcohol consumption, previous opioid use, pain intensity etc. Even within specific categories, say chronic opioid users, there is tremendous variation in sensitivity — and thus opioid requirement under various conditions.

In most situations, patients can simply be queried about pain, and their responses used to guide analgesic administration. But during anesthesia, patients do not experience pain (a conscious response). But patients nonetheless clearly experience and respond to nociception even during general anesthesia. Increases in blood pressure and heart rate roughly indicate when patients are experiencing nociceptive stress, but neither is reliable. No other routine anesthetic monitors provide useful indications of nociceptive intensity.

Even experienced anesthesiologists cannot reliably predict or estimate opioid requirements in individual patients. Consequently, most routinely give small amounts of opioid during general anesthesia, and often give a bolus of a slow-onset, long-acting opioid such as morphine or hydromorphone at the end of surgery to provide analgesia during the initial hours of post-anesthetic recovery. The doses given, while reasonable *on average*, often prove inadequate or excessive for individual patients. Those given too much awaken slowly at the end of anesthesia and may breathe poorly; those given inadequate doses suffer intense pain upon awaking and it often takes many boluses of opioid and considerable time to control their pain.

There are now several devices that estimate nociception during general anesthesia including the Surgical Pleth Index, pupillary reflexes, galvanic skin responses, and heart-rate variability.[1-4] The best-validated system is the PMD-200 system from Medasense (Ramat Gan, Israel). It is comprised of a console and designated finger probe and a single-use sensor. The PMD-200 acquires 4 signals: photoplethysmography, galvanic skin response, accelerometery, and skin temperature. Based on a random forest analysis, the device generates the NOL index.[5,6] The intended use of NOL is to assess nociception input during general anesthesia.

NOL is a unitless index that extends from 0 to 100, with values exceeding 25 indicating that patients are experiencing substantial nociceptive input.[7] Previous work in anesthetized patients has shown that NOL values are low in the absence of nociceptive input (e.g., when unstimulated) and progressively increase in response to progressively more intense stimuli (e.g., tetanic electrical stimulation, skin incision, and intubation).[6] At

this point, there are only limited data — largely unpublished — showing that titrating intraoperative opioids to NOL improves post-anesthetic recovery.

Most studies of NOL titration and recovery characteristics were conducted with remifentanil infusions, using target-controlled infusion, an opioid-dosing technique that is rarely used in the United States and not approved by the Food and Drug Administration.[6] Whether intraoperative titration will improve recovery characteristics will depend critically on the choice of opioid(s). Remifentanil is easy to titrate because the drug is potent and ultra-short acting. Patients given remifentanil are thus usually given a bolus of long-acting opioid such as morphine or hydromorphone near the end of surgery to bridge the analgesic gap between remifentanil discontinuation and arrival in the PACU. Thus, PACU recovery characteristics are largely determined by the long-acting opioid bolus timing and dosage which is given empirically and independent of NOL guidance.

Fentanyl is probably the ideal intraoperative anesthetic for NOL testing because of its intermediate and context-sensitive half-life (effect is proportional to not just dose but duration of administration). Fentanyl is initially short acting (typically 15 minutes) and thus easy to titrate. Its action is not terminated by metabolism; instead, the lipophilic drug redistributes into fat tissue. But after several hours of administration, much of the fat reservoir fills, and the drug's effect then becomes constrained by rate of metabolism, and can exceed the duration of morphine effect. Fentanyl is thus initially short acting, when titration is necessary, but then becomes long-acting and remains effective at least during the initial part of recovery. Patients who have long operations (≥2 hours) who are given the "right amount" of intraoperative fentanyl have effective pain control without use of a long acting opioid.

Specific Aims

Previous work has shown that NOL (Medasense, Ramat Gan, Israel) accurately quantifies nociception during general anesthesia.[6] Presumably, titrating opioids to NOL will therefore provide individual guidance so that patients will be given about the right amount. Patient given the right amount will presumably awaken quickly when anesthesia is done, and have good initial pain control in the PACU. To the extent that NOL titration facilitates optimal opioid dosing, patients are likely to have better PACU experiences — which would be an important outcome that clinicians and regulators are likely to take seriously.

Aim of this study:

Demonstrate that intraoperative NOL-guided titration of fentanyl improves initial recovery characteristics. All times below are relative to when sevoflurane anesthesia is discontinued.

Primary hypothesis. Pain scores (0-10 verbal response scale) at 10-minute intervals during the initial 60 minutes of recovery are less in patient with NOL-guided fentanyl than with routine care, with 1 point being considered a clinically meaningful difference

Primary Outcome. Pain Scores at 10-minute intervals during the initial 60 minutes of recovery

Secondary hypothesis. NOL patients are more likely to have a "good" pain scores, defined as < 5 (i.e., 0,1,2,3 or 4) across the measured intervals, with a relative 10% or more increase in the proportion of good scores being considered clinical meaningful.

Secondary Outcome. Whether or not the pain score at any measured interval is < 5.

We will also consider several exploratory hypotheses.

Exploratory hypothesis 1. Fewer analgesic rescue boluses are required in NOL-titrated patients during the initial 60 minutes of recovery.

Exploratory hypothesis 2. NOL-guided patients are no less alert (Ramsay score) during the initial 60 minutes of recovery than those given fentanyl per routine, based on a clinically meaningful non-inferiority delta of 20%.

Exploratory hypothesis 3. Emergence from anesthesia (discontinuation of sevoflurane anesthesia to extubation) is faster in NOL-guided patients.

Exploratory hypothesis 4. Fewer NOL-guided patients experience post-operative nausea and/or vomiting (PONV) at least once during the initial 60 minutes of recovery.

Exploratory hypothesis 5. There are fewer episodes of inadequate analgesia (too much or too little) in NOL-guided patients. Inadequate analgesia will be defined by systolic pressure ≥140 mmHg, heart rate exceeding 90 beats/min, diaphoresis, tearing, or movement. Excessive anesthesia will be defined by MAP <65mmHg or BIS < 40. All values must return to normal for at least 15 minutes for a subsequent deviation to be

considered a new episode. The outcome for a patient will be the number of episodes.

Exploratory hypothesis 6. There will be less respiratory depression during the initial 60 minutes of recovery, defined as respiratory rate <8 breaths/min or saturation <90% for at least 1 minute while on nasal cannula oxygen at 2 L/min; unplanned airway support after PACU admission (nasal trumpet, oral airway, PPV, BiPap, or intubation with a laryngeal airway or endotracheal tube); or naloxone use.

Methods

The study will be conducted with IRB approval and written informed consent. The trial will be registered at ClinicalTrials.gov before the first patient is enrolled.

Subject selection

We will enroll patients having laparoscopic major abdominal or pelvic surgery, or similarly large operations. Patients who chronically use opioids will *not* be excluded. Both men and women will be recruited, and we will encourage under-represented minorities to participate. We will enroll up to a maximum of 144 adult patients.

Inclusion criteria

1) Adults having major non-cardiac surgery expected to last ≥2 hours;
2) American Society of Anesthesiologists physical status 1-3;
3) Age 21-85 years old;
4) Planned endotracheal intubation.

Exclusion criteria

1) Planned neuraxial or regional block;
2) Clinician preference for an opioid other than, or in addition to, fentanyl;
3) Non-sinus heart rhythm;
4) Neurologic condition that, in the opinion of the investigators, may preclude accurate assessment of postoperative pain and nausea;
5) Lack of English language fluency;
6) Routine user of psychoactive drugs other than opioids;
7) Contraindication to sevoflurane, fentanyl, morphine, or ondansetron.

8) Intracranial surgery.
9) BMI > 40

Protocol

Patients will be premedicated with 0-2 mg midazolam per preference of the attending anesthesiologist. General anesthesia will be induced as preferred by the attending anesthesiologist, usually with a combination of lidocaine 1 mg/kg, propofol 1-4 mg/kg, fentanyl 1-2 µg/kg, and rocuronium 0.6-1.2 mg/kg or succinylcholine 1.5 mg/kg, as clinically appropriate. The trachea will be intubated and the lungs will be mechanically ventilated per clinical routine. General anesthesia will be maintained with sevoflurane at a target concentration of 0.7 %, with the dose being adjusted based on apparent clinical need, supplemented with fentanyl. Sevoflurane will be given per clinical routine and adjusted as usual in response to vital signs, surgical need, etc. Nitrous oxide will not be used for induction or during anesthetic maintenance. Vasopressors, antihypertensives, and drugs to control heart rate may be given as clinically indicated. Depth of anesthesia will be recorded for all patients using BIS.

Unless another opioid is clinically indicated, fentanyl will be the only opioid used for induction and throughout anesthesia. Long-acting opioids such as morphine will not be given. No opioid will be given unless clinically indicated from the end of surgery until patients reach the recovery unit.

Patients will be randomized 1:1, stratified for pre-operative chronic opioid use, with random-sized blocking to NOL guided analgesic management or routine care. The randomization table will be prepared by trial statisticians, and allocation will be concealed until shortly before anesthetic induction with a web-based randomization system.

1) **Routine opioid management.** Clinicians will be blinded to NOL monitoring and use clinical judgement to determine how much fentanyl should be given, and when. Clinical judgement will be according to their standard practice and may include interpretation of blood pressure, heart rate, diaphoresis, tearing, and pupil size. Boluses of fentanyl 1 µg/kg actual body weight (ABW), up to a maximum dose of 100 µg per bolus, can be given per clinical judgement. Towards the end of the surgery (approximately 30-45 minutes before end of surgery, based on clinical judgment), the boluses of fentanyl will be reduced to 0.5 µg/kg ABW, up to a maximum of 50 µg per boluses. Boluses will be given per clinical judgment.
2) **NOL-guided opioid administration.** Clinicians will titrate fentanyl to keep NOL under 25 — *always using good clinical judgement for individual patients*.

NOL values exceeding 25 for more than 30 seconds will typically be treated with boluses of fentanyl 1µg/kg ABW, up to a maximum of 100 µg per boluses, 5-minute intervals. Towards the end of the surgery (approximately 30-45 minutes before end of surgery, based on clinical judgment), the boluses of fentanyl will be reduced to 0.5 µg/kg ABW, up to a maximum of 50 µg per boluses, 5 minutes intervals. The target of a NOL score below 25 will be maintained until surgery ends.

Approximately 20-30 minutes before end of the surgery, a preemptive bolus of hydromorphone will be given intravenously per clinical routine;

- Patients younger than 70 years: 0.4 mg of hydromorphone for patients with an ABW <60 kg and 0.6 mg of hydromorphone for patients with an ABW > 60 kg
- Patients aged between 70 and 75 years: 0.4 mg of hydromorphone,
- Patients older than 75 years: 0.2 mg of hydromorphone.

Near the end of surgery, 4 mg ondansetron will be given intravenously per clinical routine. Upon completion of surgery, sevoflurane will be discontinued. Neuromuscular block will be reversed with sugammadex per clinician preference. At the end of the surgical procedure, patients will be extubated and transferred to the post anesthesia care unit (PACU).

Surgical pain will be treated with boluses of intravenous morphine/ hydromorphone per clinical routine by nurses blinded to intraoperative randomization. PCA will be activated upon arrival to PACU, per routine care. Generally, rescue boluses are given when verbal response pain scores are ≥4/10, but consistent postoperative analgesic management will be at the discretion of the postoperative clinical team. Nausea and vomiting will be initially treated by intravenous injection of 4mg ondansetron per clinical routine. Alternative anti-emetics will be administered as clinically indicated.

Measurements

Demographic and morphometric characteristics will be recorded, including sex, age, race, height, weight and opioid use in the last month (estimated morphine equivalents). Anesthesia clinicians cannot be blinded since they will need to titrate opioid administration to NOL. However, all postoperative care and evaluations will be fully blinded to randomization, thus preventing measurement bias. There will thus be separate teams of investigators for the intraoperative and postoperative portions of the trial.

All routine anesthetic monitoring will be used, and the results recorded electronically. Blood pressure will be evaluated continuously with an arterial catheter if clinically indicated; otherwise, blood pressure will be evaluated oscillometrically at 3-

minute intervals. Anesthetic drugs including end-tidal sevoflurane concentration, type and duration of surgery will also be recorded electronically at one-minute intervals. Inadequate analgesia will be defined by systolic pressure ≥140 mmHg, heart rate exceeding 90 beats/min, MAP<65 mmHg. Vasoactive drugs and episodes and duration of hypotension (mean arterial pressure <65 mmHg, occurrences of MAP <60 & MAP <55) will be recorded. Muscle-relaxant administration will be recorded as well.

During surgical stimulation under general anesthesia, a NOL of zero indicates no nociceptive response, and NOL of 100 indicates extreme nociceptive response. NOL values below 25 represent nociception/anti-nociception balance, suggesting either no nociception in the absence of noxious stimuli, or effective analgesia in the presence of noxious stimuli. NOL values are recorded by the Medasense monitor at 5-second intervals.

The clock on the NOL monitor will be synchronized to that driving the electronic record. Nociception will be continuously evaluated in all participating patients. However, values will be blinded to clinicians when patients are assigned to the routine opioid management group.

We will record the time of reversal agent administration wrist, the time at which sevoflurane is discontinued, along with the end of surgery (last stitch), eye opening, and extubation. Discontinuation of sevoflurane will be considered the end of anesthesia and the beginning of recovery.

The following will be recorded on the PMD-200 monitor, using the EVENTS button, as accurately as possible:

1. Medications administration:
    a. Fentanyl
    b. Vasoactive drugs
    c. Muscle relaxants
    d. Reversal agents
2. Events:
    a. Induction
    b. Intubation
    c. Foley catheter placement
    d. Incision
    e. Insufflation
    f. Trocar insertion
    g. Discontinuation of sevoflurane
    h. Extubation

In recovery, patients will be asked to rate their pain at rest on a 0-10 verbal response scale. Measurements will be taken at 10-minute intervals from awakening until 60 minutes has elapsed. Somnolent patients will be given a score of “S” for queries to which they are unable to respond. Patients will simultaneously be asked to rate nausea on a 0-10 scale. Sedation will be evaluated with the Ramsay score, also at 10-minute intervals.

Episodes of vomiting during the initial 60 minutes of recovery will be recorded. The time and dose of any administered postoperative analgesics or anti-emetics will be recorded.

The trial will end after 60 minutes of recovery and all subsequent management will be per clinical routine.

Data Analysis

Randomized groups will be assessed for balance on baseline characteristics using the standardized differences, defined as the difference in means or proportions divided by the pooled standard deviation. An absolute standardized differences > 0.10 will be considered as imbalanced. We will use modified intent-to-treat such that all randomized patients receiving any of the study intervention (either one, even if the incorrect treatment was applied) will be included in the primary analyses.

Primary outcome. We will assess the treatment effect of NOL guided analgesic management versus routine care on mean pain score with the first 60 minutes of the recovery period using a linear mixed effects model adjusting for within-patient correlation across the 7 time points, and fixed effects for intervention, time (as categorical) and the stratification variable of pre-operative chronic opioid use. [8] We will also asses the treatment-by-time interaction. We will decide on the most appropriate correlation structure empirically, using the AIC criterion, and considering either AR(1), exchangeable, or other correlation.

Sensitivity analysis. As a sensitivity analysis we will assess the treatment effect on pain score using a mixed effects proportional odds model in which we consider patient as a random effect while estimating the proportional odds ratio for patients having a better outcome on NOL than standard care, again adjusting for the stratification variable.

Secondary outcome. We will assess the treatment effect of NOL versus routine care on the proportion of patients with pain score less than 5 (i.e., 0-4) across the 7 time points using a generalized linear mixed effects model with a binary outcome (<5 or ≥5), log link

(to be able to estimate relative risk), patient as random effect and modeling the within-subject serial correlation using an R matrix (considering autoregressive AR(1), exchangeable and unstructured correlation structures), with treatment group and the stratification variable as fixed effects. We will also asses the treatment-by-time interaction. Results will be reported as the relative risk (95% CI) of having a "good" pain score over time in NOL versus routine care.

Exploratory outcome 1. We will assess the treatment effect on the first exploratory outcome of number of analgesic rescue boluses using either a negative binomial regression (for count data), or else a proportional odds logistic regression if the negative binomial distribution is not a good fit to the data. In either case we will again adjust for the stratification variable.

Exploratory Outcome 2. We will assess the treatment effect on the Ramsey score measured at 10 minute intervals for during the first 60 minutes using a mixed effects proportional odds model to adjust for the within-patient correlation in the same manner as described for the sensitivity analysis for the primary outcome. We will test whether NOL is noninferior to routine care on the Ransey score using a noninferiority delta of 1.2 for the proportional odds ratio, such that NOL will be deemed noninferior if the upper confidence limit for the odds ratio is less than 1.2. This will be accompanied by a 1-sided statistical test for noninferiority using the method described in Mascha and Sessler (2011), [9] in which we use the parameter estimate and standard error of the treatment effect from the mixed effects model as well as the noninferiority delta in the test statistic, as

$$T_{NI} = \frac{\hat{\beta}_1 - \delta}{SE_{\hat{\beta}_1}}, \text{where } \hat{\beta}_1 \text{ is the estimated log-odds ratio, } SE_{\hat{\beta}_1} \text{ is the estimated standard error, and } \delta \text{ is}$$

,

the log (delta), or log (1.2).

Exploratory Outcome 3. We will assess the treatment effect (in form of a hazard ratio) on the time to emergence from anesthesia using a Cox proportional hazards regression model adjusting for the stratification variable. We will check the proportional hazards assumption graphically and with the treatment-by-log (time) interaction. In presence if an interaction the treatment effect will be assessed using the log-rank test from a Kaplan-Meier analysis.

Sample size justification.

Pilot patients: N=21 pilot patients were enrolled prior to the start of the study to familiarize the study team with the protocol and identify any systematic issues that might result in protocol modifications. In the below sample size calculations we used data on these patients to help estimate the standard deviation of the primary outcome (pain score) and the within-subject correlation on the pain score across the 7 measurement times.

Required Sample Size. We plan the study to have 90% power at the 0.05 significance level to detect a difference in mean pain score of 1.25 or more between groups when measured over 10 minutes intervals during the first 60 minutes in the recovery period and analyzed using a linear mixed effects regression model. Based on our pilot study data (N=21) and previous work (SOLAR study report, Figure 1) we estimate the standard deviation of the pain score to be about 2.5 and the within-subject correlation to be approximately 0.60 when assumed to be exchangeable across measurements. Making these assumptions we would need a total of 116 patients before accounting for interim analyses, and a maximum of 144 after adjusting for planned interim analyses at each 1/4 of the maximum sample size. We therefore plan to randomize and enroll a maximum of 144 patients under these assumptions.

Interim analyses. We will conduct interim analyses for efficacy and futility at each 1/4 of the maximum sample size using a group sequential design and conservative gamma spending function parameters of -2 for efficacy and 0 (more aggressive) for futility. If the alternative hypothesis effect size (1.25 point difference) is true in the population sampled from, with the planned sample size we will cross an efficacy or futility boundary at each of the 4 looks with respective cumulative probabilities of 0.16, 0.50, 0.78 and 1.0.

Z-statistic boundaries for efficacy (futility) will be > 2.80 (≤ 0.156), > 2.58 (≤ 0.667), > 2.34 (≤ 1.42), and > 2.09 (≤ 2.09). The average total sample size across many simulations, assuming the alternative hypothesis is true (a true difference of 1), is N=64.

Simulations with Effect Size Larger Than Planned. With the given design and corresponding stopping rules, if the true effect size (difference of 1.25 in mean pain score) is large than planned, the probability of crossing an efficacy boundary earlier in the trial will be proportionately increased. For example, if the true difference is 1.5, the cumulative probability of crossing a boundary (either efficacy or futility) in the 1st through 4th looks will be approximately 0.21, 0.62, 0.91 and 1.0, with average total sample size across many simulations was 81 patients.

Internal Pilot Study to Reassess Standard Deviation and Within-Patient Correlation. At the second interim analysis we will conduct an internal pilot study to reassess the standard deviation and within-patient correlation using the observed data for the primary outcome. Without considering the observed treatment effect, in a blinded fashion, we will use the observed within-patient correlation from the linear mixed effects model and the standard deviation at each time point to reassess the maximum required N to have 90% power at the 0.05 significance level the detect a difference of 1.25 or more in pain score. If the required sample size is at least 10% higher than initially planned, the Executive Committee will decide whether to recommend that the maximum sample size be

increased to maintain 90% power. There is no statistical penalty for this internal pilot re-estimation of the within-patient correlation "nuisance parameter". [10]

Human Subjects Protection

The experimental device PMD-200 from Medasense, Ramat-Gan) is CE marked and has been sold and used in the European Union for 3 years, and in Canada for 2 years. However, the NOL device has yet to be submitted for FDA clearance. The proposed pilot trial is designed to provide information that will help the investigators, Medasense, and the FDA optimally design a Phase 3 multi-center trial that might support FDA approval.

Typical pain scores during the initial phase of post-anesthetic recovery at the Cleveland Clinic Main Campus are 7/10, indicating poor pain control. The only aspect of our protocol that is non-standard is opioid titration to NOL. Pain scores could hardly be worse with NOL guidance, and in all cases, clinical judgement will prevail. Standard vital signs monitoring will continue to be used per current routine care. Our experienced anesthesia attending will never give patients clearly inadequate or excessive doses.

An important consideration is that opioid under-dosing and over-dosing is easily correctable. Most patients at the Cleveland Clinic and world-wide are under-dosed (as indicated by typically high initial pain scores) which is ameliorated simply by giving additional opioid. Over-dosing is also not especially serious since opioids can be antagonized by administration of small repeated doses naloxone until the right residual opioid effect remains. We thus request a non-significant risk device exemption for the proposed pilot trial.

Supplemental material includes sedation and delirium instruments, CE certificates, and safety and design documentation.

The following Adverse Events (AE) will be collected:

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

Pre-planned interventions or occurrence of endpoints, including deviations in vital signs, specified in the CIP are not considered AEs, if not defined otherwise

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

Where the definition indicates “device”, it refers to the PMD-100.

Table 1. Definition of Adverse Events and Device Deficiency

Term	Abbreviation	ISO Definition
Adverse Event	AE	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. *NOTE 1:* This definition includes events related to the investigational medical device or the comparator. *NOTE 2*: This definition includes events related to the procedures involved. *NOTE 3:* For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect	ADE	Adverse event related to the use of an investigational medical device. *NOTE 1:* This definition includes adverse events resulting from insufficient or inadequate instructions for use, installation, operation, or any malfunction of the investigational medical device. *NOTE 2:* This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Device Effect	SADE	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Serious Adverse Event	SAE	An adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in: • a life-threatening illness or injury, • a permanent impairment of a body structure or a body function, • in-patient or prolonged hospitalization, • medical or surgical intervention to prevent life-threatening illness or injury or

Term	Abbreviation	ISO Definition
		permanent impairment to a body structure or a body function, • led to fetal distress, fetal death or a congenital abnormality or birth defect. *NOTE:* Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Unanticipated Serious Adverse Device Effect	USADE	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
Device Deficiency	DD	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE:* Device deficiencies include malfunctions, use errors, and inadequate labelling.

Reporting procedures

AE information will be collected throughout the study and reported to Medasense on an AE eCRF, one for each adverse event. It is the responsibility of the investigator to identify the occurrence of adverse events to ensure that the information is accurately documented in the medical record and on the eCRFs.

DD information will also be collected throughout the study and reported to Medasense on a Device Deficiency eCRF. DDs require immediate reporting if they did not lead to an adverse event but could have led to a serious adverse device effect (SADE):

- if either suitable action had not been taken,
- if intervention had not been made, or
- if circumstances had been less fortunate

AE documentation will include the following information at a minimum:

- Date of event
- Time of the event
- Diagnosis and description
- Actions taken / treatment (including vital signs, and date and time of rescue related actions when applicable)
- Assessment of seriousness
- Relatedness to the device
- Outcome or resolution and date of the resolution

For AEs that require immediate reporting, initial reporting may be done by phone, fax, e-mail, or preferably on the eCRF completing as much information as is available. The completed AE eCRF must be sent to Medasense as soon as possible.

In case the investigator requires information from the sponsor in an emergency situation, the investigator can contact Medasense team directly.

The sponsor will ensure timely Adverse Event reporting to meet global regulatory requirements.

Table 2. Reporting Requirements for Events

Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE):	
Investigator submit to:	
Medasense	Immediately after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Serious Adverse Events (SAE)	
Investigator submit to:	
Medasense	Immediately after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.

EC/IRB	Submit to EC/IRB per local reporting requirement.
Adverse Device Effects (ADE)	
Investigator submit to:	
Medasense	Immediately after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
All other AEs	
Investigator submit to:	
Medasense	Submit in a timely manner after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Device Deficiency with SADE potential	
Investigator submit to:	
Medasense	Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency.
Regulatory Authorities	As per local reporting requirement.
EC/IRB	As per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	As per local reporting requirement.
EC/IRB	As per local reporting requirement.
All other Device Deficiencies	
Investigator submit to	
Medasense	Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory Authorities	As per local reporting requirement.
EC/IRB	As per local reporting requirement.

Supplemental Material

1) Richmond Alertness and Agitation Scale.
2) 3D Confusion Assessment Method for delirium.
3) Australian Register of Therapeutic Goods Certificate
4) EC Certificate
5) Medical Device License Canada
6) ISO Certificate
7) User Manual
8) Declaration Latex free raw material
9) Phthalate free declaration
10) RoHS Declaration 2019
11) Risk Management Plan
12) Evaluation of the NOL Index- Clinical Validation Studies
13) Clinical Evaluation Report
14) Summative Usability Validation Report

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List of changes to the study protocol:

Version 2 (03-29-2020)

- Inclusion criteria: we now specify, that all patients receive a Morphine PCA as clinical standard postoperatively.
- Exclusion criteria: BMI > 40 kg/m^2 was added.
- Protocol: we now specified that sevoflurane concentration will be maintained at a target concentration of 0.7%, consistent with good clinical judgement.
- Protocol: we now specify for the NOL-guided opioid administration group, that NOL values above 25 exceed 60 or more seconds, before a fentanyl bolus should be given.
- Protocol: we now specify, that all patients will receive a morphine PCA, which will be activated upon arrival to PACU, per routine care.
- Measurements: we now define inadequate analgesia: inadequate analgesia will be defined by systolic pressure ≥140 mmHg, heart rate exceeding 90 beats/min, MAP<65 mmHg. Vasoactive drugs and episodes and duration of hypotension (mean arterial pressure <65 mmHg, occurrences of MAP <60 & MAP <55) will be recorded. Muscle-relaxant administration will be recorded as well.
- Measurements: we now define documented medications and measurements in more details: The following will be recorded on the PMD-200 monitor, using the EVENTS button, as accurately as possible: Medications administration: Fentanyl, Vasoactive drugs, Muscle relaxants, Reversal agents; Events: Induction, Intubation, Foley catheter placement, Incision, Insufflation, Trocar insertion, Discontinuation of sevoflurane, Extubation.
- We added two paragraphs about Adverse Events and Reporting procedures.

Version 3 (11/03/2020)

- Title: “benefits” was replaced by “consequences”
- Several Co-investigators have been added.
- Aims and hypothesis have been revised.
- Methods: subject selection. “We will enroll up to 144 adult patients.” (replaced 30 cases)
- Inclusion criteria: “Morphine PCA as clinical standard postoperatively” was removed and is now considered optional
- Number of pilot patients: we will now enroll up to 25 pilot patients (replacing 10 patients)
- Study protocol: Routine opioid management. We now specify the bolus of fentanyl: “Boluses of fentanyl 1 µg/kg actual body weight (ABW), up to a maximum dose of 100 µg per bolus” …Towards the end of the surgery (approximately 30-45 minutes before end of surgery, based on clinical judgment), the boluses of fentanyl will be reduced to 0.5 µg/kg ABW, up to a maximum of 50 µg per boluses. Boluses will be given per clinical judgment.
- Study protocol: NOL guided opioid administration. We now specify the bolus of fentanyl.”NOL values exceeding 25 for more than 30 seconds will typically be treated with boluses of fentanyl 1µg/kg ABW, up to a maximum of 100 µg per boluses, 5-minute intervals. Towards the end of the surgery (approximately 30-45 minutes before end of surgery, based on clinical judgment), the boluses of fentanyl will be reduced to 0.5 µg/kg ABW, up to a maximum of 50 µg per boluses, 5 minutes intervals. The target of a NOL score below 25 will be maintained until surgery ends.”
- Study protocol: NOL-guided opioid administration. Time above a NOL threshold above 25 exceeding 30 seconds (replaced 60 seconds).
- Study protocol: NOL-guided opioid administration. “Boluses of fentanyl 1 µg/kg actual body weight (ABW), up to a maximum dose of 100 µg per bolus”
- Study protocol: we now standardize the preemptive bolus of opioid at the end of surgery: Approximately 20-30 minutes before end of the surgery, a preemptive bolus of hydromorphone will be given intravenously per clinical routine;

- Patients younger than 70 years: 0.4 mg of hydromorphone for patients with an ABW <60 kg and 0.6 mg of hydromorphone for patients with an ABW > 60 kg
- Patients aged between 70 and 75 years: 0.4 mg of hydromorphone,
- Patients older than 75 years: 0.2 mg of hydromorphone.

- The section on statistical analysis has been entirely revised.