# PCRC Proposal Cover Sheet

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| Title of Study or Project: | Perioperative Opioid Use – Correlating Patterns of Utilization |
| Primary Institution: | University of Michigan |
| Principal Investigator: | M. Burns |
| Co-Investigators: | J. Gong, J. Vandervest, D. Colquhoun, A. Thompson, L. Saager, N. Shah, J. Wiens, S. Kheterpal, C. Brummett |
| Type of Study: | Retrospective Observational |
| IRB Number/Status: | HUM00156358 (in process) |
| Hypothesis: | We hypothesize that perioperative opioid use correlates to continued use for post-operative in-hospital care. We will study the heterogeneity of opioid delivery intraoperatively and associated outcomes and applying machine learning models to understand opioid administration practices and correlate these practices with opioid use post-operatively. |
| Number of Patients/Participants: | All valid cases from all sites contributing data to MPOG . |
| Power Analysis: | None required |
| Proposed statistical test/analysis: | Machine learning techniques will use training, validation, and holdout set separation. |
| Resources (Brief summary of resources for data collection, personnel, financial): | Programmer to pull the data and statistical analysis. |

# Perioperative Opioid Use – Correlating Patterns of Utilization

M. Burns, J. Gong, J. Vandervest, D. Colquhoun, A. Thompson, N. Shah, L. Saager, J. Wiens, S. Kheterpal, C. Brummett and colleagues

# Background

Opioid use and prescriptions around medical visits is a major focus in healthcare. Opiates and opioids top the list of “problem drugs” which cause the most disease burden and drug-related deaths worldwide and there has been a rapid increase in the medical prescription and use of opioid medications in the United States over the past two decades[1]. One single-center tertiary care medical center study found that greater than 1 in 4 patients reported opioid use upon presenting for surgery[2]. The understanding of the heterogeneity of opioid administration in medical facilities important and guidelines for perioperative opioid use continue to be in need of supportive evidence. Clinical practice guidelines from the American Society of Regional Anesthesia and Pain Medicine released in 2016 found only 4 of the 32 recommendations were supported with high-quality evidence and 11 recommendations were made on the basis of low-quality evidence[3].

Understanding opioid administration is important to help improve perioperative care. The majority of research has focused on understanding opioid use within and outside the hospital at times surrounding operative procedures. An equivalency is often used to compare and convert opioid use called Oral Morphine Equivalency (OME). OME conversions are limited to medications routinely used outside of the operating room (OR) and omit some critical medications and routes used within the OR. We have developed a new algorithm at the Multicenter Perioperative Outcomes Group (MPOG) to incorporate medications used intraoperatively. This equivalency is a tool to help understand opioid use in the operating room. Quantifying opioid use is challenging as potencies vary across routes and agents. By applying the concept of OME, our design focused on quantification and conversion of all opioids used in the perioperative setting. The MPOG registry has collected over 10 million anesthesia records across over 50 institutions. We identified all opioid – unit of measure – route combinations across all MPOG cases. Bolus and infusion (including weight and time based units) were converted to total drug dose in mg. These medications were then converted to a common OME using previously published results[4-8].

The pathways to addiction and treatment are poorly understood and it is unknown what type of role perioperative opioid exposure plays. The first step in investigating this complicated question of association is to better understand the heterogeneous exposure patients have to opioids within healthcare, and as anesthesiologists it is important to understand these exposures during operations. With a better understanding of different practice approaches, we can explore opioid exposure in the context of individual health states of patients. Characterizing heterogeneity across providers and practices can help us identify patterns, improve guidelines, and influence policy change to inhibit the misuse of opioids.

## Specific Aims

We hypothesize there is variation in opioid perioperative administration in clinical practice. We aim to investigate potential variation between institutions, within institutions, and between providers accounting for variation in patient and case demographics. We aim to explore possible associations of opioid administration variation with case outcomes.

**Aim 1. Characterize heterogeneity in anesthesiology provider opioid administration by provider and by institution between similar case groupings.** Using case level, provider level, and institution level perioperative EHR data we will divide cases into similar groupings based on case-specific data (ex. CPT billing codes, procedure text, case duration, case location, etc.). We aim to identify variation in practice patterns comparing institutions and a separate analysis comparing providers within each institution. We will utilize OME calculations as well as type of medication and route data as outcomes for comparison.

Aim 1a: Describing OME tool, technical aspects (including dashboard), quality use and impact

Aim 1b: Provide descriptive data of OME and opioid administration variation across sites and define opioid administrative groups

Aim 1c: Provide descriptive data of OME and opioid administration variation across providers within institutions and case types and define opioid administrative groups

**Aims 2 and 3. Explore possible correlations between opioid administration heterogeneity and case outcomes.** In this aim we will look to identify possible correlation between case outcomes (listed as primary and secondary outcomes) and variation in opioid administration practice. We will additionally investigate heterogeneity within procedures as time series and try to identify dosing patterns intraoperatively. Overall, we will aim to further characterize variations in practice (similar to Aim 1) and additionally attempt to find possible correlations to potential case outcomes.

Aim 2a: Provide descriptive data of intraoperative OME/opioid administration across institutions within case groupings looking at characteristics of medication dosing in relation to operative patient data (vital signs, fluid balances, medications previously administered)

Aim 2b: Investigate potential correlations of clinical variation from 2a to individual perioperative outcomes including use of machine learning predictive modeling

Aim 3a: Provide descriptive data of intraoperative OME/opioid administration across providers within case types and within institutions looking at characteristics of medication dosing in relation to operative patient data (vital signs, fluid balances, medications previously administered)

Aim 3b: Investigate potential correlations of clinical variation from 3a to individual perioperative outcomes including use of machine learning predictive modeling

# Methods

## Patient Population (Inclusion Criteria)

The study population will consist of all procedural cases, adult and children, documented in the MPOG database which contain one of the following anesthesia CPT codes as the primary anesthesia CPT:

### Cardiac

- Cardiac surgery with pump and > 1 year old (CPT: 00562)
- Cardiac surgery with hypothermic arrest (CPT: 00563)
- CABG with pump (CPT: 00567)
- Heart Transplant (CPT: 00580)
- CABG without pump (CPT:00566)

### Spine

- Cervical spine and cord; not otherwise specified (CPT: 00600)
- Cervical spine and cord; patient in sitting position (CPT: 00604)
- Thoracic spine and cord; not otherwise specified (CPT: 00620)
- Thoracic spine and cord; thoracolumbar sympathectomy (CPT: 00622)
- Thoracic spine and cord, via an anterior transthoracic approach; not utilizing 1 lung ventilation (CPT: 00625)
- Thoracic spine and cord, via an anterior transthoracic approach; utilizing 1 lung ventilation (CPT: 00626)
- Lumbar region; not otherwise specified (CPT: 00630)
- Lumbar region; lumbar sympathectomy (CPT: 00632)
- Lumbar region; diagnostic or therapeutic lumbar puncture (CPT: 00635)
- Extensive spine and spinal cord procedures (eg, spinal instrumentation or vascular procedures) (CPT: 00670)

### Upper Abdomen

- Intraperitoneal - upper abdomen including laparoscopy; not otherwise specified (CPT: 00790)
- partial hepatectomy or management of liver hemorrhage (excluding liver biopsy) (CPT: 00792)
- Intraperitoneal - upper abdomen including laparoscopy; pancreatectomy, partial or total (eg, Whipple) (CPT: 00794)
- Intraperitoneal - upper abdomen including laparoscopy; gastric restrictive procedure for morbid obesity (CPT: 00797)

### Lower Abdomen

- Procedures in lower abdomen including laparoscopy; not otherwise specified (CPT: 00840)
- Procedures in lower abdomen including laparoscopy; abdominoperineal resection (CPT: 00844)
- Procedures in lower abdomen including laparoscopy; pelvic exenteration (CPT: 00848)

### Hysterectomy

- Intraperitoneal procedures in lower abdomen including laparoscopy; radical hysterectomy (CPT: 00846)
- Vaginal procedures (including biopsy of labia, vagina, cervix or endometrium); vaginal hysterectomy (CPT: 00944)

Major Vascular

- Anesthesia for procedures on major lower abdominal vessels; not otherwise specified (CPT: 00880)
- Anesthesia for procedures on major lower abdominal vessels; inferior vena cava ligation (CPT: 00882)

Knee/Popliteal

- Open or surgical arthroscopic procedures on knee joint; total knee arthroplasty (CPT: 01402)

Hip

- Open procedures involving hip joint; total hip arthroplasty (CPT: 01214)

## Exclusion Criteria

- We will exclude cases that have incomplete or duplicate records and cases not including CPTs listed in the Inclusion Criteria (above).

## Primary Outcomes

Our first primary outcome will be defined as statistically and clinically relevant variation of opioid administration. We are interested in 2 approaches when looking at institutions: one looking across all institutions with comparison to a procedural group median value, and a second looking at individual comparisons between institutions within procedural groups. A separate primary outcome will be looking at variation from the median among providers within institutions and within procedural groups. We plan to investigate creation of opioid administrative groups within the analysis of variation.

We plan to correlate OME with all other primary outcomes and we plan to compare specific medications and variation grouping (as determined within the study) with all other primary outcome frequencies.

Significant clinical variation will be defined as practice variation >25% from the overall median. Also a difference of 25% in pairwise comparisons between institutions. Please see our statistics section for our definition of statistical significance.

Secondary outcome analysis will be used to investigate frequency of individual secondary outcomes to overall OME and opioid administrative groups.

For clinical outcomes we plan to evaluate the following measures:

- Oral Morphine Equivalency (OME)
- Respiratory ICD 9/10 complication bundles
- Opioid reversal (naloxone)
- Respiratory rate vitals at end of case after documented 4/4 and muscle relaxant reversal
- Reintubation prior to anesthesia end

## Secondary (exploratory) Outcomes

- Procedural case duration
- 30-day in hospital mortality
- Length of stay
- Post procedure location (admission type)
- ICD 9/10 complication bundles

## Key Features (Variables) to be Extracted:

| Variable | Phenotype | ConceptID | Notes |
|---|---|---|---|
| **Demographics** | | | |
| Age | AgeInYears | | |
| Gender | Sex | | |
| Height | Height | | |
| Weight | Weight | | |
| BMI | BMI | | |
| Elixhauser Comorbidities | ElixhauserComorbidity (all start with "TL") | | There are 31 in total |
| ASA Class | ASAClass_cleaned | | |
| Emergency Status | EmergencyStatus_YesNo | | |
| Institution | Institution | | |
| PreOp Pain Score | | 71000 | |
| Home Medications | | 71210 | |
| Controlled Substance Agreement | | 50176 | |
| ICD Opioid Abuse History | | | [F11.1% and 30550-30553%] (abuse), [F11.2%, 30403%] (dependence), [ [T40.0-T40.4%, 9650%] (overdose or poisoning by heroin, methadone, other opiates and related narcotics), [3047% and F19.2%] (opioid in combination with another drug dependence) |

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|---|---|---|---|
| ICD Opioid Use History | | | [F11.9%(use)] |
| ICD Amphetamines History | | | [F15.1%, 30570-30573%] (amphetamine abuse), [F15.2%, 30440-30443%] (amphetamine dependence), [T43.62%, 969.72] (Poisoning by amphetamines), [F15.2%, 3044%] (amphetamine dependence), [F14.1%, 30560-30563%] (cocaine abuse), [F14.9%] (cocaine dependence), [T40.5%, 97081%] (cocaine poisoning, adverse effects) |
| ICD Antidepressant History | | | [305.8%] (abuse), [T43.0%-T43.2%, 969.0%] (poisoning), F19.1% (other psychoactive abuse) substance abuse), F19.2% (other psychoactive substance dependence) |
| **Case Info** | | | |
| Procedure Text (cleaned) | ProcedureTextCleaned | | |
| Procedure Text | ProcedureText | | |
| Primary Anesthesia CPT | PrimaryAnesthesiaCPT | | |
| Predicted Anesthesia CPT | PrimaryAnesthesiaCPT_Predicted | | |
| Case Start | CaseStart | | |
| Case End | CaseEnd | | |
| Case Duration | CaseDuration | | |
| Anesthesia Start | AnesthesiaStart | | |

| | | | |
|---|---|---|---|
| Anesthesia End | AnesthesiaEnd | | |
| Anesthesia Duration | AnesthesiaDuration | | |
| Induction End | InductionEnd | | |
| Surgery Start | SurgeryStart | | |
| Surgery End | SurgeryEnd | | |
| Extubation Times | ExtubationTimes | | |
| Extubated in PACU | | 50376 | |
| Patient Extubated | | 50202 | |
| Patient NOT Extubated | | 50128 | |
| Vent Start | VentStartEnd | | |
| Vent End | VentStartEnd | | |
| Anesthesia Technique | All “AnesthesiaTechnique” collations | | |
| Arterial Line | ArterialLinePlaced | | |
| ETT | EndotrachealTube | | |
| Weekend | Weekend | | |
| Holiday | Holiday | | |
| EBL | EBL | | |
| Urine Output | UrineOutput | | |
| Crystalloids | Crystalloids | | |
| Colloids | Colloids | | |
| PRBCs | PRBCMLDerived | | |
| Cryo | CryoprecipitateMLDerived | | |
| FFP | FFPMLDerived | | |
| Attending Staff ID (primary) | PrimaryProvider | 6000 | Return the actual ID for the case |
| Resident ID (primary) | PrimaryProvider | 6001-6004 | Return the actual ID for the case |
| CRNA ID (primary) | PrimaryProvider | 6005 | Return the actual ID for the case |
| Surgeon IDs | | `MPOG_Staff_Role_Concept_ID = 6006` | Return ALL actual IDs for the case |
| Surgeon IDs (secondary) | | `6012` | Return ALL actual IDs for the case |
| Surgical Resident | | 6007 | Return ALL actual IDs for the case |
| Attending Staff IDs | | 6000 | Return ALL actual IDs for the case |
| Anesthesia Fellows | | 6014 | Return ALL actual IDs for the case |

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|---|---|---|---|
| Resident IDs | | 6001-6004 | Return ALL actual IDs for the case |
| CRNA IDs | | 6005 | Return ALL actual IDs for the case |
| Anesthesia Assistants | | 6010 | Return ALL actual IDs for the case |
| OralMorphineEquivalent | OralMorphineEquivalent | | |
| OME_Norm | OralMorphineEquivalentNormalized | | |
| Non-Opioid Analgesics | NonOpioidAnalgesics | | |
| Case Vital Signs | | | All vitals for each case: BP (non-invasive and arterial), HR, RR, EtCO2 |
| Vent Settings | | | Vent mode – mainly need to know if the patient is breathing spontaneously |
| Case Medications | | | Need all case meds, dose, time, route, and unit of measure administered for the case (including inhaled anesthetics) |
| Quality Measure Results | CombineMeasureResults | | |
| CP Bypass Duration | CardioPulmonaryBypassDuration | | |
| CP Bypass Start | CardioPulmonaryBypassStart | | |
| CP Bypass Stop | CardioPulmonaryBypassStop | | |
| **Outcomes** | | | |
| AKI | AKI | | |
| Complication Bundles | All collations labeled “complication” | | |
| Length of Stay | HospitalLOSDays | | Quality? |
| Admission Type | AdmissionType | | |
| 30-day Mortality | HospitalMortality30Day | | |
| Last Known Alive | | | |
| Train of Four | | 3330 | Is there a way they process these in the measures? |
| Naloxone | | 10312 | |
| Neostigmine | | | Date/time, unit of measure, dose, route |

| | | | |
|---|---|---|---|
| Sugammadex | | | Date/time, unit of measure, dose, route |
| Double-lumen tube used | | | Airway notes and text search within these notes |
| Reintubation | | | Done in another study? |

## OME Tool Description

We will describe the technical build of the OME tool in detail, identifying key points in building the tool. This creation involved many clinical and technical decisions which have been well defined and will be communicated in this study. We will discuss the development of the OME quality feedback tool, currently used in quality feedback metrics for select sites. We will show dashboard views and displays of aggregate de-identified data.

## Descriptive Opioid Administration Variation

### Aggregate Case Evaluation

We will stratify cases by CPT grouping as outlined in the inclusion criteria. We will aggregate opioid within each case as sum totals, irrespective to time or dose of individual medicine administrations, using the OME conversion tool. We will identify and evaluate variation in practice across institutions and separately across providers as defined in the outcomes and statistical methods sections. We will investigate data for statistical and clinical variation across procedure groups between institutions. This analysis will categorize medication administration groups such as inclusion/exclusion of remifentanil, spinal or epidural routes of administration, and opioid-free analgesia techniques. Patient demographics and subjective measures such as pain scores will be incorporated as outcomes where data is available.

Opioid administration groups may be defined by frequency. These groups will be further analyzed. One such case grouping we are interested in investigating is the “opioid-free analgesia” case grouping in which the case was conducted without opioid administration.

Many cases have more than one provider involved, thus we will incorporate analyses using a single provider for each role defined as the one with the longest time signed into the case by time in minutes in addition to using all providers listed as involved.

### Intraoperative Case Evaluation

In a separate analysis, we will look specifically into the time, dose/unit of measure, and route of administration for each opioid medication during each individual case. Similar to aggregate case analysis we aim to identify opioid administration groups defined on frequencies. We will use time series individually as well as relative to standard operative time stamps such as anesthesia start/end, surgery start/end, and induction end. Intraoperative vital signs and non-opioid medications will be used in time

series analysis for variation of care analysis as well as machine learning methods investigating practice variation and predictive modeling.

## Opioid Administration and Outcomes

We will be interested in identifying opioid administration patterns within practice and potential correlation to patient demographics and potential case outcomes. Frequencies of outcomes between institutions, providers, and case groupings will be analyzed. Additionally, individual case outcomes will be analyzed by frequency between aggregate and intraoperative variation groups.

We are aware of a limitation of data in the data where medication administration (including opioid reversal (naloxone)) will be limited as data may only incorporate administration between anesthesia start and end, omitting administration during post-op care. ICD 9/10 complication bundles will be used as defined within the MPOG phenotype groupings. Respiratory rate vitals will be captured throughout the case; we plan to isolate respiratory rates at end of each case after documented muscle relaxant reversal (sugammadex or neostigmine administration). Reintubation prior to anesthesia end will be defined by using date/time stamp of intubation note after extubation note, but omitting cases in which a double-lumen tube was used.

## Machine Learning Methods

Perioperative opioid administration is a complex interaction of many factors: patient attributes (e.g., pain perception, opioid metabolism), case attributes (e.g., surgical procedure, surgical team), and opioid administration. We are interested in understanding how physicians treat and respond to signals of pain in the perioperative setting. We will use machine learning approaches to relate patient and case attributes with *pain treatment*. Through this process, we can better understand treatment variability in individuals with similar demographics and similar procedures; this can help lend insight into variations in perioperative opioid administration by different physicians, and it can also potentially help us better understand differences in opioid metabolism.

As a first step in this process, we plan to explore patterns of physician treatment in terms of timing during the procedure, dose, and duration in isolation from patient attributes. We will explore descriptive statistics, and use unsupervised learning techniques when necessary, to understand the main modes of variability in physician treatment actions. The goal of this step is to gain an initial understanding of how much variability exists within procedure classes and across procedure classes. This type of analysis seeks to understand a coarse notion of variation without considering dependence on patient/case-specific attributes. We will use similar methods to gain an understanding of subtypes of patients, even within those who are receiving similar procedures.

Next, we plan to relate time-series data of patient physiological signals (heart rate, blood pressure, respiratory rate, blood saturation, and end-tidal CO2) during the operative period to physician treatment actions (e.g., changes in dose/infusion, administration of bolus, administration of naloxone) using a *supervised* framework. We will take into consideration possible covariates such as fluid status (EBL, urine output, fluid administrations). We will explore various ways to model time-series, including convolutional neural networks, recurrent neural networks, and probabilistic graphical models. This model will learn relationships between physiological changes in the patient with opioid administration

decisions made by the anesthetist. This model will enable prediction of future actions based on physiological changes. This is one way to characterize what the *expected* action of the anesthesiologist will be to physiological changes, given a particular set of patient and case attributes. We will divide our data into a 60/20/20 training/validation/holdout split. Training data will be used to train the model, and the validation data will be used to tune model parameters. Final performance will be evaluated on the holdout set. After demonstrating that our model generalizes well to unseen data, we will use the model predictions to represent *expected* actions and analyze the differences between what was observed and what was expected to understand variations in provider behavior.

### Anticipated Limitations

Our proposed research study has anticipated limitations. One limitation is in the accuracy of the institutional data. We will hand audit outlier statistics and cases for validity. To prevent possible misinterpretation of data and its dissemination we will involve individual institution champions to aid in information release. Another limitation is case variability in documentation / data entry between institutions. We will limit representation using a minimal threshold for each query result. Another limitation is within the OME conversion tool itself. The conversions used within the tool were compiled from literature whose results were found using pharmacologic/pharmacokinetic studies, which may not reflect accurate human clinical care conversions.

Home medications listed in the preoperative H&P are limited and often erroneous. For example, some institutions may list a post-op med as a pre-op med as the prescription was written before the case started. This can lead to errors in our analysis and as a result we are including ICD 9/10 use/abuse data to help with determining patient preoperative opioid use.

## Statistical Analysis

Exploratory Data Analysis (EDA) techniques such as histograms, QQ-Plots, box-plots, scatterplots and basic descriptive (means, medians, IQR) will be used to assess the distribution of dependent measures. These will be used to identify the distribution of outcomes which in turn will be conductive to determining the appropriate modeling strategies. In addition, these techniques will also be used to explore the most informative transformations of the covariates, confounders and relevant predictors considered in the analysis.

SAS version 9.4 will be used for all non-machine-learning statistical analysis.

**Aim 1a: Describing OME tool, technical aspects (including dashboard), quality use and impact**

No statistical techniques are needed for this aim.

**Aim 1b: Provide descriptive data of OME and opioid administration variation across sites and define opioid administrative groups**

Oral morphine equivalents will be analyzed separately for each procedural category by institution, and will be summarized as either means (standard deviation) or median [25th to 75th percentile], as appropriate. The frequency of patients > 75th percentile of OME for each institution will be reported. Pairwise comparisons of mean or median OME between institutions will be conducted utilizing either Student's t-tests or Mann-Whitney U tests, as appropriate. Institutional practice patterns will likewise be compared between those with non-opioid analgesia vs. those with opioid analgesia, those with remifentanil use vs. those without remifentanil use, and those with a neuraxial technique vs. those without a neuraxial technique. Finally, the OME from individual opioids will be compared both within and between institutions, and will be visualized using a bubble plot to define opioid administrative groups.

A p-value of $< 0.05 / (8 \text{ procedure types}) = 0.006$ will be considered statistically significant for this analysis.

**Aim 1c: Provide descriptive data of OME and opioid administration variation across providers within institutions and case types and define opioid administrative groups**

Within an institution and procedural category, comparisons of the mean or median OME between providers will be conducted utilizing either ANOVA tests or Kruskal Wallis tests, as appropriate. The frequency of providers with a mean or median OME usage > 75th percentile will be reported. Provider practice patterns will likewise be compared between those with non-opioid analgesia vs. those with opioid analgesia, those with remifentanil use vs. those without remifentanil use, and those with a neuraxial technique vs. those without a neuraxial technique.

A p-value of $< 0.05 / (8 \text{ procedure types}) = 0.006$ will be considered statistically significant for this analysis.

**Aim 2a: Provide descriptive data of intraoperative OME/opioid administration across institutions within case groupings looking at characteristics of medication dosing in relation to operative patient data (vital signs, fluid balances, medications previously administered)**

A multivariable mixed-effects linear regression model will be constructed for each procedure type with the outcome of OME and independent variables of intraoperative vital signs, fluid balances, and medications previously administered. Variation between institution will be assessed with the random effect of institution in the model. Intra-class correlation coefficients with 95% confidence intervals will be reported for the model random effects.

Before model construction, all possible independent variables will be assessed for collinearity using a Pearson's correlation matrix. This pairwise analyses will be complemented with a Variance Inflation (VIF) analysis to determine joint-collinearity. A correlation > 0.7 between two variables is considered to be collinear. Any variable pairs deemed to be collinear will either be combined into one concept, or the variable with the largest univariate effect size will be retained in the model. All other variables will be eligible for model inclusion.

Any variable that is statistically significant in the model will be deemed to be independently associated with oral morphine equivalents. Beta coefficients and standard error will be reported for all model variables.

A p-value of $< 0.05 / (8 \text{ procedure types}) = 0.006$ will be considered statistically significant for this analysis.

**Aim 2b: Investigate potential correlations of clinical variation from 2a to individual perioperative outcomes including use of machine learning predictive modeling.**

Any variables deemed to be independently associated with OME will be included in a Spearman's partial correlation as a covariate, separately for each procedure type. The correlation will be constructed with the variables OME and each primary and secondary outcome. A correlation of $> 0.6$ will be considered a strong correlation between OME and the primary or secondary outcome, after adjusting for relevant covariates.

For supervised machine learning models, we will evaluate our approach against sensible baseline methods. To evaluate statistical significance of differences between our proposed model and baseline approaches, we will bootstrap the holdout set 1000 times and evaluate each model on each of the bootstrapped samples. These results can be used to construct a 95% confidence interval around the performance on the actual holdout set. When we are interested in a particular adverse outcome that has a large class imbalance, we will stratify the bootstrap sampling to maintain the same class presence in the bootstrapped sets as in the real holdout set. We will use a paired t-test to compare the proposed model's performance against the baseline method(s) on the bootstrapped sets. When appropriate, we will correct for multiple hypothesis testing and set an appropriately conservative statistical significance threshold.

**Aim 3a: Provide descriptive data of intraoperative OME/opioid administration across providers within case types and within institutions looking at characteristics of medication dosing in relation to operative patient data (vital signs, fluid balances, medications previously administered)**

Within institution and procedure category, a multivariable mixed-effects linear regression model will be constructed with the outcome of OME and independent variables of intraoperative vital signs, fluid balances, and medications previously administered. Variation between provider will be assessed with the random effect of provider in the model. Intra-class correlation coefficients with 95% confidence intervals will be reported for the random effects.

Before model construction, all possible independent variables will be assessed for collinearity using a Pearson's correlation matrix. This pairwise analysis will be complemented with a Variance Inflation (VIF) analysis to determine joint-collinearity. A correlation $> 0.7$ between two variables is considered to be collinear. Any variable pairs deemed to be collinear will either be combined into one concept, or the variable with the largest univariate effect size will be retained in the model. All other variables will be eligible for model inclusion.

Any variable that is statistically significant in the model will be deemed to be independently associated with oral morphine equivalents. Beta coefficients and standard error will be reported for all model variables.

A p-value of < 0.05 / (8 procedure types) = 0.006 will be considered statistically significant for this analysis.

**Aim 3b: Investigate potential correlations of clinical variation from 3a to individual perioperative outcomes including use of machine learning predictive modeling**

Any variables deemed to be independently associated with OME for each model in aim 3a will be included in a Spearman's partial correlation as a covariate, separately for each institution and procedure type. The correlation will be constructed with the variables OME and each primary and secondary outcome. A correlation of > 0.6 will be considered a strong correlation between OME and the primary or secondary outcome, after adjusting for relevant covariates.

For supervised machine learning models, we will evaluate our approach against sensible baseline methods. To evaluate statistical significance of differences between our proposed model and baseline approaches, we will bootstrap the holdout set 1000 times and evaluate each model on each of the bootstrapped samples. These results can be used to construct a 95% confidence interval around the performance on the actual holdout set. When we are interested in a particular adverse outcome that has a large class imbalance, we will stratify the bootstrap sampling to maintain the same class presence in the bootstrapped sets as in the real holdout set. We will use a paired t-test to compare the proposed model's performance against the baseline method(s) on the bootstrapped sets. When appropriate, we will correct for multiple hypothesis testing and set an appropriately conservative statistical significance threshold.

Pairwise Comparisons to identify patterns of associations

Although pairwise comparisons[9] are a useful way to fully describe the pattern of mean differences (and so, to test our research hypothesis), performing multiple analyses also creates a problem for us. There are two opposing approaches to what we should do about either increasing in the possibility of making Type I error when we make multiple comparisons. The first of these views emphasizes protection from Type I error. It is often labeled as "conservative", in that it requires extra evidence (lower p-value) to reject H0: for pairwise comparisons. The second view emphasizes protection from Type II error. It is often referred to as emphasizing "sensitivity", because it uses the a=.05 criterion for each pairwise comparison. Researchers often differ (quite loudly) about which of these approaches has greater merit, usually based on whether they are more concerned about "missing effects" (making Type II errors -- these folks usually favor sensitive pairwise testing) or "claiming to find effects that aren't really there" (making Type I errors -- these folks usually favor conservative pairwise testing). These difference become even more apparent in descriptive analysis, where the main focus in is identifying patterns of associations rather that their magnitude. Because of these differences of opinion, we chose to use a more "sensitive" pairwise comparisons, called the Least Significant Difference (LSD) procedure, and one for completing "conservative" pairwise comparisons, called the Honestly Significant Difference

(HSD) procedure. The protected Fisher's least significant difference test does not completely control the family-wise type I (false positive) error rate. Instead it chooses to maximize the power of detecting true effects while allowing the family-wise type I error rate to grow slightly larger than the alpha significance cutoff. If decisions are based on a falsely positive effect, future experiments and production outcomes will likely show no change based on that effect. If true differences are missed due to low power and their factors allowed to vary across the tested range, at best, production will be plagued by unexplained variation, and at worst an opportunity to optimize the process will have been missed. These are the most appropriate methods to consider when 'pattern" identification are of essence to the analysis.

### Missing Data

We will use exclusion or imputation, as appropriate.

## Human Subjects' Risks and Data Protection

Data analysis will be restricted to aggregated group data. Data will be de-identified regarding individual hospitals, unless specifically discussed and approved by individual hospitals for their own internal use. While hospital and hospital characteristics might be part of the analysis to account for practice variation, no individual hospitals will be identifiable in the results or publication, again discussed and approved by individual hospitals for their own internal use. Each group will contain a sufficient number of hospitals and cases to ensure de-identification or no group analysis will be performed. Again, data analysis and results will not allow identification of individual contributing sites.

Data will be maintained on a password protected secure MPOG server hosted. The study data will be accessible only to the statistical team directly involved with analyzing the data. The system fully meets all applicable HIPAA privacy and security rules. Access to the database and backups are strictly monitored according to need.

The final dataset will contain no patient or caregiver identifier. No protected health information or identifying information about individual patients, caregivers or hospitals will be part of a publication.

## Impact

Overall, this work enables the measurement and analysis of variation in the delivery of opioid medications within anesthetic care. This can inform future work on investigation into potential correlations between intraoperative opioid administration and subsequent hospital opioid administration, discharge prescriptions, and home use. This information could be useful in developing safe and effective plans for perioperative pain control.

In future work, we can build on the proposed work, optimizing knowledge of variation in care. This work will lay the groundwork for future research directions in understanding effectiveness of perioperative opioid administration. Additionally, this would could begin investigation into potential discrepancies between pharmacologic/pharmacokinetic opioid conversions and clinical care.

The results of our investigation in variation of care could be used by individual hospitals and their providers to aid in continued medical education, develop institutional care guidelines, and facilitate preparation of future anesthetic care plans.

Finally, the time series analysis and ML modeling could be utilized across additional medical specialties outside of anesthesiology. This project, if successful, will provide a framework for retrospective and predictive analysis within future related projects.

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