PCRC Proposal Cover Sheet

Title of Study or Project:	Multicenter Review of Practice Patterns Regarding Benzodiazepine Use in Cardiac Surgery
Primary Institution:	University of Michigan
Principal Investigator:	Allison Janda, MD
Co-Investigators:	Allison Janda, MD; Jessica Spence, MD; Timur Dubovoy, MD; Emilie Belley-Côté, MD PhD; Graciela Mentz, PhD; Sachin Kheterpal, MD, MBA; Michael Mathis, MD
Statisticians:	Graciela Mentz, PhD
Type of Study:	☑ Retrospective Observational
IRB Number and Status:	HUM00167369 / approved
Hypotheses/Aims:	We propose to explore data from cardiac surgical patients meeting inclusion criteria, to describe benzodiazepine use during cardiac surgery across MPOG centers. We aim to identify patient factors associated with benzodiazepine use and further describe the timing of administration. We hypothesize that patient, provider, and institutional factors are independently associated with benzodiazepine use during cardiac surgery.
Number of Patients/Participants:	Based on the availability of pertinent perioperative data, we expect approximately 5,000 patients to be included at the University of Michigan, and 60,000 in MPOG.
Power Analysis:	Sample size for this descriptive study are based on the accuracy of the overall estimates of benzodiazepine administration. It was determined that if the true population level use of benzodiazepines ranges between 70% and 90%, we will need a sample between 1,536 to 3,585 patients to estimate descriptive statistics with a precision of 3%.
Proposed statistical test/analysis:	We will produce descriptive statistics including: histograms, mean/median, standard deviation/interquartile ranges, percentiles and Q-Q plots.
Resources (Brief summary of resources for data collection, personnel, financial):	Data collection will include MPOG database queries performed via IT support. Statistical analysis will be conducted by Anesthesiology Department staff in consultation with Graciela Mentz; and in discussion with all co-investigators. Financial support as per the University of Michigan Department of Anesthesiology, NIH-NIGMS, Grant T32GM103730-06; NIH-NHLBI, Grant 1K01HL141701-02, Bethesda, MD

TITLE PAGE

Multicenter Review of Practice Patterns Regarding Benzodiazepine Use in Cardiac Surgery

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Introduction

There is remarkable variability in clinical practice and a lack of consensus amongst anesthesiologists providing care for cardiac surgery patients on a number of fronts. One area of variability in practice for cardiac anesthesiologists is the topic of benzodiazepine administration. There is weak evidence for and against benzodiazepine use in cardiac surgery, and gaps exist in the current literature in determining the impact of intraoperative benzodiazepine use and selection of induction agents on postoperative outcomes.[1,4] Some studies focusing on administration of benzodiazepines in the intensive care unit (ICU) have shown that benzodiazepines are associated with an increased risk of delirium or disrupted neurocognitive recovery after surgery.[1–3,5–8] Since there is little clarity on the impact of intraoperative benzodiazepines, benzodiazepine use is often dogmatic and is debated. Some anesthesiologists utilize benzodiazepine-sparing techniques due to the evidence in the ICU population relating benzodiazepine use to delirium,[1,2,5,7,8] but some anesthesiologists specifically administer benzodiazepines for their amnestic properties due to a higher than average rate of intraoperative awareness in the cardiac surgery population.[1,4,14–16] A survey of cardiac anesthesiologists in Canada found that 89 percent of respondents did routinely use benzodiazepines, yet, a majority believed most cardiac anesthetics could safely be performed without benzodiazepines.[1] Although work has been done in the intensive care unit regarding the impact of benzodiazepine use, and practice patterns in Canada have been identified via survey,[1] little is known about practice patterns in the United States.

In this descriptive study, we will use the electronic health record of multiple US institutions to describe practice patterns regarding benzodiazepine use including prevalence of use, total dosage, and context of benzodiazepine use during the perioperative period for cardiac surgical cases. We hypothesize that patient, provider, and institutional factors are independently associated with benzodiazepine use during cardiac surgery. These data will inform practice benchmarking and design of prospective randomized trials evaluating the relationship between intraoperative benzodiazepine administration and delirium, morbidity, and mortality, with randomized clinical trials.

Methods

Study Design

This is a retrospective observational study which will follow STROBE reporting guidelines.[17] Study outcomes and statistical methods were established and will be presented and approved at a multicenter peer-review committee prior to extraction of data and data analysis. This study was approved by the University of Michigan Institutional Review Board (HUM00167369, Ann Arbor, Michigan). As no care interventions were involved and all protected health information except date of service and extremes of age were removed prior to analysis, patient consent was waived. A revised finalized proposal was registered on Open Science Framework on, XXXX prior to accessing study data.

Study Population

The study population includes patients in the MPOG database from 24 MPOG participating institutions performing greater than 200 cardiac cases per year, from January 1, 2014-August 1, 2019.

Inclusion Criteria

- Adult patients (>18 years) undergoing elective or urgent cardiac surgical procedures from January 1, 2014 - August 1, 2019
- Arterial line used
- General anesthesia with an endotracheal tube used

Exclusion Criteria

- Patients <18 years of age
- Lung transplants, and transcatheter procedures
- ASA Class 6
- Case Duration < 120 minutes

Excluded for Primary Analysis (included in *a priori* subgroup analyses):

- Cases with a mechanical support device present, i.e. intra-aortic balloon pump, ECMO, or VAD (pre-existing or implanted), open aortic procedures, and heart transplants

- ASA Class 5

Data source

Data will be obtained from the Multi-Center Perioperative Outcomes Group (MPOG) dataset after the MPOG peer-review research committee's approval. Data acquisition through uploads of electronic medical record systems from each participating institution, data storage, and secure transfer has been previously described.[18,19]

Primary Outcome

The primary outcome will be any exposure to benzodiazepines in the perioperative period as a dichotomous variable. Benzodiazepine exposure is defined as the administration of a bolus or infusion of midazolam, alprazolam, diazepam, clonazepam, or lorazepam at any point between one hour before anesthesia start and anesthesia end or documented in the anesthesia record. An *a priori* subgroup analysis will also be performed for those patients who underwent cardiac surgery and met inclusion and exclusion criteria for our primary outcome, but did not receive benzodiazepines to assess patient, provider, surgical, and institutional factors associated with a lack of benzodiazepine administration.

Secondary Outcomes

Secondary outcomes will include dose of benzodiazepines standardized as midazolam equivalents as a continuous variable (Table 1).[20–23] Distribution of dosing will be assessed using histograms, QQ-plot and box plots to determine symmetry, normality and potential extreme values. We will also examine benzodiazepine administration timing to elucidate whether the benzodiazepine was given prior to anesthetic induction or as a propofol-sparing amnestic during the intraoperative period as a secondary analysis. To distinguish between low and high administration of benzodiazepines, the continuous variable of total dose will be examined using a histogram, and modes will be assessed (for example, one mode at 2mg and another mode at 10mg). Based on inspecting the histogram we can then create clinically meaningful ranges of low and high use of benzodiazepines and will perform an *a priori* subgroup analysis using these clinically relevant ranges. To elucidate the temporal patterns of benzodiazepine administration, the perioperative period will be divided into two general windows: 1) the pre-induction period,

and 2) the intraoperative period. If bypass is used, as it is for most cases we will examine, the intraoperative period will be further divided into pre-bypass, bypass, and post-bypass periods to allow for higher granularity for determining the timing of benzodiazepine administration. These timing windows are further described in Table 2.

Covariates

Covariates for these assessed outcomes will include, patient age, sex, race, BMI, ASA status, surgical procedure type, duration of surgery, year of procedure, Elixhauser comorbidities (hypertension, coronary artery disease, congestive heart failure, arrhythmia, valvular heart disease, pulmonary circulation disorders, diabetes, neurologic disorders, renal failure, liver disease, obesity, psychotic disorders, depression, and chronic pulmonary disease), history of alcohol use, history of drug abuse, preoperative outpatient benzodiazepine use, preoperative outpatient opioid use, preoperative mechanical ventilation, first recorded mean arterial pressure in the OR and preoperative vasopressor or inotropic infusions as a marker for hemodynamic instability, administration of alternative induction agents such as etomidate, ketamine, and propofol, administration of opioids, anesthesia provider ID, and institution ID. Due to the likely institutional factors component of the culture of benzodiazepine use, we will also cluster institutions by region, and alternatively, by academic or university associated hospitals relative to private or non-university associated hospitals.

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 dosing outcomes which in turn will be conducive 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. Outlier values will be rejected if outside of the valid ranges as described in MPOG phenotypes.

Continuous measures will be summarized in terms of means and standard deviation if the distribution is symmetric or medians and interquartile range if not. Binary and categorical measures will be summarized using a percentage. Tests of differences of means, medians or

proportions will be done using ANOVA F-test, Wilcoxon rank sum or logistic types of approaches respectively. If institutions with extremes of use or low case volumes prevent model convergence, they will be included for the descriptive analysis, but will be excluded from the model. Low case volumes would be defined as <125 cases per year, consistent with the 2011 American College of Cardiology Foundation/American Heart Association Task Force Guidelines.[20]

Variance between providers at a population level and institutional level, patients at a population level and an institutional level, and institutions will also be assessed using intraclass correlation coefficients (ICCs) and median odds ratios. The goal of this analysis is to describe the proportion of total variance in the outcome that is attributable to that factor.

Secondary outcome and a priori subgroup analyses

The secondary outcomes will be analyzed separately. For the assessment of total dose of benzodiazepines, the various benzodiazepines administered includes lorazepam, alprazolam, diazepam, clonazepam, and midazolam. The most common benzodiazepine used is likely midazolam. If midazolam accounts for 90% or greater of benzodiazepine use, midazolam will be used as our primary analysis and any other benzodiazepines administered will be examined as a secondary analysis. If there is greater variability in type of benzodiazepine administered, each benzodiazepine will be standardized as midazolam equivalents (Table 1) to incorporate the other utilized benzodiazepines in the total dose analysis.[21-24] For the timing of benzodiazepine administration outcome, the perioperative period will be divided into windows of pre-induction and intraoperative periods. The induction medications will be included in the intraoperative group. If bypass was used, the intraoperative period will be further divided into pre-bypass, bypass, and post-bypass periods. The definitions for these time windows for data extraction can be found in Table 2.

An *a priori* subgroup analysis will also be performed for those patients who underwent cardiac surgery and met inclusion and exclusion criteria for our primary outcome, but did not receive benzodiazepines to assess patient, provider, surgical, and institutional factors associated with a lack of benzodiazepine administration. To further transform the continuous dosing data into a clinically relevant binary variable to compare low versus high benzodiazepine administration, we will perform an *a priori* subgroup analysis on low versus high benzodiazepine use. The cut off or range of low and high benzodiazepine use will be determined by inspection of a histogram of the total dose administered for each case, and we will define clinically

meaningful ranges for this *a priori* subgroup analysis based on modes of use to avoid an arbitrary preset cut off which may not have clinical relevance. The cut offs and ranges will be determined during data inspection, but prior to data analysis. Additionally, we will perform an *a priori* subanalysis including additional cardiac cases that are typically associated with hemodynamic instability such as ASA 5s, VADs, IABPs, other mechanical support devices, heart transplants and ascending aortic procedures to determine the association between these procedures and benzodiazepine use within this subset of patients.

Power analysis

Descriptive studies power analysis and sample size determination are based on the accuracy of the prevalence estimates. In order to estimate the true proportion of Benzodiazepine administered, p, within a 3% accuracy (or precision) we use the 95%CI for the sample proportion. The formula for the 95%CI is

$$p \pm 1.96*SE(p)$$

Where SE(p) is the standard error of the proportion. The formula for SE(p) has the square root of n, the sample size, in the denominator. Therefore, as the sample size gets bigger, SE(p) gets smaller, the 95%CI gets narrower, and we get a more precise estimate of the true population prevalence of benzodiazepine use. Table 3 and Figure 1 outlines estimated sample sizes with variable power and accuracy.

Based on this analysis we expect that either in the single, where p=0.99 with n=5,260 or in the multicenter center case, p=0.89 with n=63,601, we will be able to estimate the true population level benzodiazepine use with 1 or 2% accuracy (Table 3, and Figure 1).

Handling of missing or invalid data

Missing data patterns will be assessed and the percent of missing data will be determined. If missing data is larger than 10 percent, multiple imputation techniques will be used to complete that data in order to estimate unbiased statistical parameters.

Preliminary Data

A MPOG DataDirect query was performed (MPOG Query ID 1991), showing 63,601 cases meeting criteria, 56,305 (88.7%) of which included administration of benzodiazepines.

A single-center query was performed at the University of Michigan (MPOG Query ID 1993), showing 5,260 cases meeting criteria, 5,182 (98.5%) of which included administration of benzodiazepines.

Areas for discussion/known limitations

There are several limitations for this retrospective descriptive study. The most notable limitation includes the ability to accurately capture data greater than one hour prior to the start of the case. We agree that some institutions may administer benzodiazepines greater than one hour preoperatively as part of sedation for a procedure (i.e. arterial line placement), or multiple hours before the procedure as an IV or PO medication as an anxiolytic, but these will not be captured reliably within the given database. Therefore, we will limit preoperative data to one hour prior to anesthesia start to avoid the issue of inappropriately designating “missing” data as an absence of benzodiazepine administration when it could have been administered, just not recorded in the available data. Due to limitations inherent in retrospective data analysis on a large scale, we will rely on data inspection prior to any analysis to reveal additional limitations and will describe the issues as they are encountered.

This study assesses one aspect of practice variability among anesthesiologists for cardiac surgery and we plan to assess others in this list in the near future. What other areas might be interesting targets for future studies? Topics with variability in practice patterns and controversial thresholds could include:

- Vasopressor / inotrope use and dosage
- Fluid management / use of albumin / autologous blood removal
- Pump flow while on cardiopulmonary bypass
- Ventilation strategies / supplemental oxygen administration
- Neuromuscular blockade management / timing of reversal
- Use of advanced hemodynamic monitors, e.g. pulmonary artery catheter
- Neuroprotection strategies, use of BIS/NIRS monitoring
- Induction agent selection

Table 1. Midazolam Equivalent Conversion Table

Benzodiazepine	Equivalent dose (mg) per 1mg IV Midazolam
Midazolam (IV mg)	1mg
Diazepam (IV, mg)[22, 23]	2.5mg
Diazepam (oral, mg)[25]	2.5mg
Alprazolam (oral, mg)[24]	0.25mg
Clonazepam (oral, mg)[24]	0.25mg
Lorazepam (IV, mg)[21]	0.5mg

Dose equivalents derived from previously published literature.[21-25]

Table 2. Cardiac Surgery Stages

Overlapping Phase of Care	Start Time	Stop Time
Entire Case	MPOG Case Start Phenotype *	MPOG Case End Phenotype *
Pre- induction	1. 1 hour prior to anesthesia start; if not available then 2. 1 hour before patient in room; if not available then 3. 1 hour before MPOG Case Start Phenotype	1. Patient in room; if not available, then 2. 10 minutes after anesthesia start (10 minutes elapsed)
Intraoperative	1. Patient in room; if not available then 2. 5 minutes before first ventilator start time; if not available then 3. 10 minutes elapsed after anesthesia start	1. Anesthesia end
Pre-Cardiopulmonary Bypass	1. If CPB was used, patient in room; if not available then 2. 5 minutes before first ventilator start time; if not available then 3. 10 minutes elapsed after anesthesia start	1. Cardiopulmonary bypass start
Cardiopulmonary Bypass	1. First cardiopulmonary bypass start	1. Last Cardiopulmonary bypass end
Post-Cardiopulmonary Bypass	1. Last Cardiopulmonary bypass end	2. Anesthesia end

* Available at https://collations.mpogresearch.org/

Table 3. Estimated sample sizes with variable power and degree of accuracy.

	Sample Size			
Required Degree of Accuracy	p=0.70	p=0.80	p=0.9	p=0.95
1%	32,269	24,586	13,829	7,299
2%	8,067	6,146	3,427	1,825
3%	3,585	2,731	1,536	811
4%	2,016	1,536	864	456
5%	1,290	983	553	291
6%	896	682	384	202
7%	658	501	282	150
8%	504	384	216	114
9%	398	303	170	90
10%	322	245	138	73

Where, p = true proportion of benzodiazepine administered.

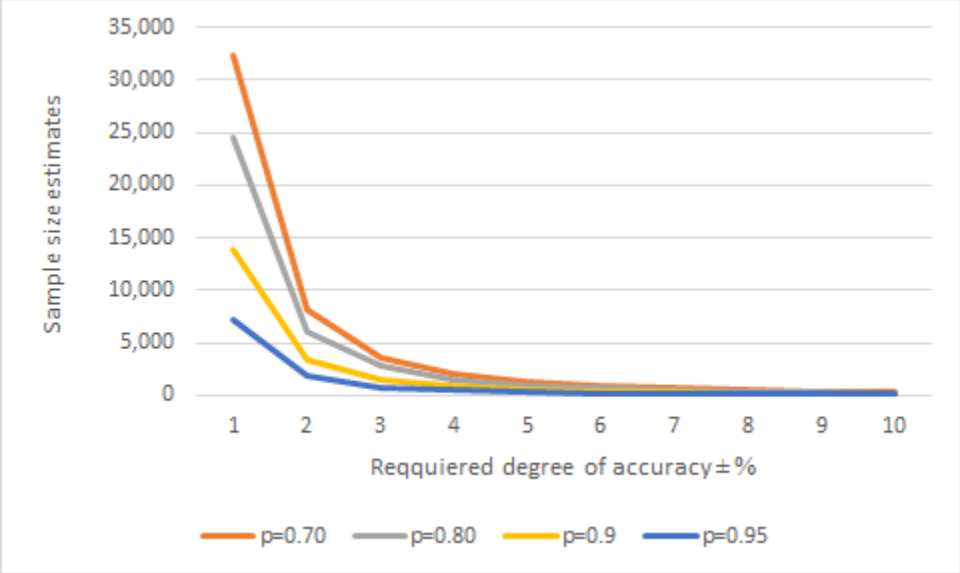

Figure 1. Sample size estimates with variable power and degree of accuracy.

MPOG Query ID: 1991

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Query Specification – Inclusion Criteria

Variable Name	Definition	Data Format	Data Source / ID	Notes
DOS	Date of Surgery/Procedure/Service	Mo/Day/Year	Phenotype: Surgery Start Date/Time	Include: Surgery performed between January 1, 2014 and August 1, 2019
Age	Age in years	Num	Phenotype: Age (Years)	Include: >/=18
MPOG_Institution_ID	MPOG Institution ID	Num	Phenotype: Institution	Recode MPOG institution ID into a fake institution ID
Cardiac_cases	Cardiac cases	Num	Phenotype: Cardiac	Include: o Cardiac – Anesthesia CPT Codes 00550, 00560, 00561, 00562, 00563, 00567, 00580

Query Specification – Exposure Variables, Covariates, Exclusion Criteria, and Outcomes

Variable Name	Definition	Data Format	Data Source / ID	Notes
DOS	Date of Surgery/Procedure/Service	Mo/Day/Year	Phenotype: Surgery Start Date/Time	Include: Surgery performed between January 1, 2014 and August 1, 2019
Age	Age in years	Num	Phenotype: Age (Years)	Valid range: 18-120
Sex	Sex	Num	Phenotype: Sex	Sex
Race	Patient Race	Num	Phenotype: Race	Race
Actual_Procedure_Text	Procedure name (performed, not scheduled)	Character	Phenotype: Procedure Text	Actual_Procedure_Text
Charge_Capture_Primary_ Diagnosis_Code	ICD-9/ICD-10 Code	Num	All ICD diagnosis codes	Charge_Capture_Primary_ Diagnosis_Code
MPOG_Patient_ID	MPOG Patient ID Number	Char		MPOG_Patient_ID
MPOG_Case_ID	MPOG Case ID Number	Char		MPOG_Case_ID
MPOG_Institution_ID	MPOG Institution ID	Num	Phenotype: Institution	MPOG_Institution_ID

Cardiac_cases_per_year	Number of cardiac cases per year	Num	Number of Phenotype: Cardiac =1 per year	Cardiac_cases_per_year_2014 Cardiac_cases_per_year_2015 Cardiac_cases_per_year_2016 Cardiac_cases_per_year_2017 Cardiac_cases_per_year_2018 Cardiac_cases_per_year_2019
MPOG_Primary_Provider_ID	MPOG Primary Provider, attending only	Num	Phenotype: PrimaryProvider	MPOG_Primary_Provider_ID
MPOG_Starting_Provider_ID	MPOG Starting Provider, attending only	Num	Phenotype: StartingProvider	MPOG_Starting_Provider_ID
Primary_Anesthesia_CPT	Primary anesthesia base CPT	Character	Phenotype: Primary Anesthesia CPT	Primary_Anesthesia_CPT
Predicted_Anesthesia_CPT	Predicted anesthesia CPT	Number	Anesthesia CPT prediction tool	Predicted_Anesthesia_CPT
MPOG_Admission_Type	Integer representing patient admission type	Num	Phenotype: Admission Type	MPOG_Admission_Type
MPOG_Primary_Procedural_ Service_Concept_ID	Integer representing primary procedural service	Num	MPOG Surgical Services by code	MPOG_Primary_Procedural_ Service_Concept_ID
MPOG_Primary_Procedural_ Service_Concept_Desc	Description associated with concept identifier above	Char	MPOG Surgical Service by name	MPOG_Primary_Procedural_ Service_Concept_Desc
ASA_Class_Number	ASA classification	Num	Phenotype: ASA Class (cleaned)	ASA_Class_Number
Emergent	Processed emergent status	Yes / No	Phenotype: Emergency Status (ASA Class) Yes/No	Emergent
General_yn	General anesthetic technique used	Yes / No	Phenotype: Anesthesia Technique: General	General_yn
Anesthesia_Start_DT	First date/time when anesthesia start documented	Mo/Day/Year HH:MM	Phenotype: Anesthesia Start	Anesthesia_Start_DT
Anesthesia_End_DT	Last date and time when anesthesia end documented for case	Mo/Day/Year HH:MM	Phenotype: Anesthesia End	Anesthesia_End_DT

Patient_In_Room_DT	First date/time when patient in room documented	Mo/Day/Year HH:MM	Phenotype: Patient In Room Date/Time	Patient_In_Room_DT
Patient_Out_Of_Room_DT	Last date/time when patient transport from room documented for case	Mo/Day/Year HH:MM	Phenotype: Patient Out Of Room Date/Time	Patient_Out_Of_Room_DT
Ventilator_Start_DT	Date and time of ventilator start time	Mo/Day/Year HH:MM	Phenotype: Ventilator Start Time	Ventilator_Start_DT
Bypass_Start_DT	First date/time when cardiopulmonary bypass start documented for case	Mo/Day/Year HH:MM	Phenotype: Cardiopulmonary Bypass Start	Bypass_Start_DT
Bypass_End_DT	Last date/time when cardiopulmonary bypass end documented for case	Mo/Day/Year HH:MM	Phenotype: Cardiopulmonary Bypass End	Bypass_End_DT
Bypass_Duration	Duration of bypass in minutes from start to end	Num	Phenotype: Cardiopulmonary Bypass Duration	Bypass_Duration
Case_Duration_In_Room_min	Minutes from patient in room to patient out of room	Num	Phenotype: Patient In Room Duration	Case_Duration_In_Room_min
Case_Duration_Anesthesia_min	Minutes from anesthesia start to end	Num	Phenotype: Anesthesia Duration	Case_Duration_Anesthesia_min
Case_Duration_Surgery_min	Minutes from procedure start to procedure end	Num	Phenotype: Surgery Duration	Case_Duration_Surgery_min
Meds_Preop	List of preop medications – used to generate Home_Benzo_YN and Home_Opioid_YN	List of Char	Phenotype: PreopMedications	Meds_Preop; used to generate Home_Benzo_YN and Home_Opioid_YN
PMH_Elix_CHF	History of Congestive Heart Failure, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Congestive Heart Failure	PMH_Elix_CHF

PMH_Elix_Arrhythmia	History of Cardiac Arrhythmia, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Cardiac Arrhythmia	PMH_Elix_Arrhythmia
PMH_Elix_Valvular	History of Valvular Disease, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Valvular Disease	PMH_Elix_Valvular
PMH_Elix_Pulm_Circ	History of Pulmonary Circulation Disorder, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Pulmonary Circulation Disorders	PMH_Elix_Pulm_Circ
PMH_Elix_HTN_Uncomp	History of Uncomplicated Hypertension, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Hypertension (uncomplicated)	PMH_Elix_HTN_Uncomp
PMH_Elix_HTN_Comp	History of Complicate, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Hypertension (complicated)	PMH_Elix_HTN_Comp
PMH_Elix_Neuro	History of Other Neurological Disorders, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Other Neurological Disorders	PMH_Elix_Neuro
PMH_Elix_CPD	History of Chronic Pulmonary Disease, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Chronic Pulmonary Disease	PMH_Elix_CPD

PMH_Elix_Diabetes_Uncomp	History of Uncomplicated Diabetes, using Elixhauser Comorbidity Enhanced ICD-9-CM Algorithm	Yes/No	Phenotype: Comorbidity - Diabetes (uncomplicated)	PMH_Elix_Diabetes_Uncomp
PMH_Elix_Diabetes_Comp	History of Complicated Diabetes, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Diabetes (complicated)	PMH_Elix_Diabetes_Comp
PMH_Elix_Renal_Failure	History of Renal Failure, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Renal Failure	PMH_Elix_Renal_Failure
PMH_Elix_Liver_Disease	History of Liver Disease, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Liver Disease	PMH_Elix_Liver_Disease
PMH_Elix_Obesity	History of Obesity (part of Elixhauser Comorbidity Enhanced ICD-9-CM), however will use MPOG to detect	Yes/No	Phenotype: Comorbidity - Obesity	PMH_Elix_Obesity
PMH_Elix_EtOH	History of Alcohol Abuse, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Alcohol Abuse	PMH_Elix_EtOH
PMH_Elix_Drug_Abuse	History of Drug Abuse, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity - Drug Abuse	PMH_Elix_Drug_Abuse

PMH_Elix_Psychoses	History of Psychoses, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity-Psychoses	PMH_Elix_Psychoses
PMH_Elix_Depression	History of Depression, using Elixhauser Comorbidity Enhanced ICD-9-CM and ICD-10 Algorithms	Yes/No	Phenotype: Comorbidity-Depression	PMH_Elix_Depression
MPOG_Height_cm	MPOG processed height in cm via most recent height in cm, or converted from inches if not available	Num	Phenotype: Height (cm)	MPOG_Height_cm
MPOG_Weight_kg	MPOG processed weight in kg via most recent weight in kg, or converted from pounds if not available	Num	Phenotype: Weight (kg)	MPOG_Weight_kg
MPOG_Body_Mass_Index	MPOG BMI calculated from MPOG height and weight	Num	Phenotype: BMI	MPOG_Body_Mass_Index
MPOG_WHO_BMI_ Classification_CD	WHO BMI Classification code from MPOG BMI	Num	Phenotype: WHO BMI Classification	MPOG_WHO_BMI_ Classification_CD
Baseline_MAP	Baseline Mean Arterial Pressure	Num	Phenotype: Baseline Blood Pressure - Mean	Baseline_MAP
Midazolam	Midazolam given as infusion and bolus; date, time, and dose for each administration in a separate table; total dose for the preop period, total dose for intraop period	Num, Mo/Day/Year HH:MM	MPOG Concept: 10301	Midazolam
Lorazepam	Lorazepam given as infusion and bolus; date, time, and dose for each administration in a separate table; total dose	Num, Mo/Day/Year HH:MM	MPOG Concept: 10272	Lorazepam

	for the preop period, total dose for intraop period			
Diazepam	Diazepam given as infusion and bolus; date, time, and dose for each administration in a separate table; total dose for the preop period, total dose for intraop period	Num, Mo/Day/Year HH:MM	MPOG Concept: 10154	Diazepam
Clonazepam	Clonazepam given as infusion and bolus; date, time, and dose for each administration in a separate table; total dose for the preop period, total dose for intraop period	Num, Mo/Day/Year HH:MM	MPOG Concept: 10700	Clonazepam
Alprazolam	Alprazolam given as infusion and bolus; date, time, and dose for each administration in a separate table; total dose for the preop period, total dose for intraop period	Num, Mo/Day/Year HH:MM	MPOG Concept: 10721	Alprazolam
Fentanyl	Fentanyl as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10186	Fentanyl_YN Fentanyl_inf_max Fentanyl_bolus_total
Remifentanil	Remifentanil as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10390	Remifentanil_YN Remifentanil_inf_max Remifentanil_bolus_total
Sufentanil	Sufentanil as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10414	Sufentanil_YN Sufentanil_inf_max Sufentanil_bolus_total

Alfentanil	Alfentanil as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10020	Alfentanil_YN Alfentanil_inf_max Alfentanil_bolus_total
Methadone	Methadone as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10290	Methadone_YN Methadone_inf_max Methadone_bolus_total
Hydromorphone	Hydromorphone as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10219	Hydromorphone_YN Hydromorphone_inf_max Hydromorphone_bolus_total
Morphine	Morphine as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10306	Morphine_YN Morphine_inf_max Morphine_bolus_total
Propofol	Propofol as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10377	Propofol_YN Propofol_inf_max Propofol_bolus_total
Etomidate	Etomidate as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10183	Etomidate_YN Etomidate_inf_max Etomidate_bolus_total
Ketamine	Ketamine as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as	Y/N, num for infusion, Num for bolus	MPOG Concept: 10238	Ketamine_YN Ketamine_inf_max Ketamine_bolus_total

	bolus, sum of total bolus doses			
Phenylephrine	Phenylephrine as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10354	Phenylephrine_YN Phenylephrine_inf_max Phenylephrine_bolus_total
Norepinephrine	Norepinephrine as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10326	Norepinephrine_YN Norepinephrine_inf_max Norepinephrine_bolus_total
Vasopressin	Vasopressin as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10445	Vasopressin_YN Vasopressin_inf_max Vasopressin_bolus_total
Dopamine	Dopamine as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10165	Dopamine_YN Dopamine_inf_max Dopamine_bolus_total
Dobutamine	Dobutamine as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10162	Dobutamine_YN Dobutamine_inf_max Dobutamine_bolus_total
Epinephrine	Epinephrine as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10176	Epinephrine_YN Epinephrine_inf_max Epinephrine_bolus_total

Isoproterenol	Isoprotere as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10235	Isoproterenol_YN Isoproterenol_inf_max Isoproternol_bolus_total
Milrinone	Milrinone as a Y/N variable; if given as an infusion, max infusion rate for the case; if given as bolus, sum of total bolus doses	Y/N, num for infusion, Num for bolus	MPOG Concept: 10302	Milrinone_YN Milrinone_inf_max Milrinone_bolus_total

PCRC Proposal Submission Checklist

Pre-submission preparation:

- [x] Proposal reviewed with institution's MPOG Site PI: Mike Mathis
- [x] Proposal discussed with MPOG Coordinating Center member: Mike Mathis
- [x] Institutional IRB Complete; IRB number: HUM00167369
- [x] Cohort Sample Size Estimated using MPOG DataDirect Query
- [x] Test data download of local data performed. If infeasible, explain:

PCRC proposal components:

Manuscript

- [x] Cover Sheet (limit one page)
- [x] Introduction (target 300-500 words; limit 750 words)
- [x] Methods - including acknowledgement of appropriate guidelines for reporting (e.g. STROBE, TRIPOD, etc.)
- [x] Proposed Statistical Analyses

Query Specifications

- [x] Data elements to determine inclusion criteria - MPOG Query ID: see query spec
- [x] Data elements to perform analysis - MPOG Query ID: see query spec

Reporting

- [x] Completed checklist from appropriate guidelines for reporting (e.g. STROBE, TRIPOD, etc.)

On behalf of the proposed team of investigators, I attest to having completed the above required steps prior to scheduling a PCRC review.

Name: Allison Janda Date: 10/9/19

Role (e.g. first author, PCRC presenter, site PI/RC): First Author