PCRC Proposal Cover Sheet

Title of Study or Project:	The Epidemiology and Impact of Medication Errors in the Perioperative Setting
Primary Institution:	University of Michigan
Principal Investigator:	Mark S. Hausman, Jr., MD
Co-Investigators:	Michelle Housey, MPH, Sachin Kheterpal, MD, MBA
Type of Study:	☐ Retrospective Observational
IRB Number/Status:	HUM00102384(UM Performance Site) HUM00103730 (UM Coordinating Center)
Hypothesis:	Perioperative medication errors occur not infrequently, and may result in meaningful incremental healthcare resource consumption and patient harm. This study seeks to: 1) Determine the epidemiology of perioperative medication errors utilizing NCC MERP taxonomy and standardized definitions. 2) Determine the consequences of errors in terms of added healthcare resource consumption and patient harm.
Number of Patients/Participants:	With 8 participating centers we anticipate 800-1200 patients with reported medication errors, and an additional 800-4800 matched controls.
Power Analysis:	Post hoc power analysis to be completed once the absolute drug errors are known
Proposed statistical test/analysis:	Overall incidence of self-reported perioperative medication errors will be determined. Annual incident rates will be assessed in aggregate and at the institutional level. Univariate descriptive statistics will classify medication errors. Matched cases and controls will be compared to determine associations between patient outcomes with medication errors.
Resources (Brief summary of resources for data collection, personnel, financial):	The Multicenter Perioperative Outcomes Group, Information Technology Department at University of Michigan. Department of Anesthesiology, University of Michigan. This study will be done in partnership with Becton, Dickenson and Company, who will provide financial support as well as participate in the study conception, design, and manuscript preparation.

The Epidemiology and Impact of Medication Errors in the Perioperative Setting

Introduction:

Preventable medical errors have been estimated to account for between 44,000-98,000 patient deaths per year, and an estimated 7% of all hospital admissions experience a serious medication error. [1] A recent review article found a median medication error rate of 19.6% in health care settings worldwide. [2] Medication errors are of particular focus in the perioperative setting due to the acuity of patients and the classes of medications being administered. In fact, perioperative medication errors are three times more likely to cause harm than non-perioperative medication errors. [3] 39-94% of anesthesia providers surveyed have acknowledged committing a medication error in the past, [4] [5] [6] [7] [8] which may reflect the unique feature of anesthesia practice where providers prescribe, dispense and dose medications largely without pharmacist or nurse review.

Despite the potency of perioperative medication errors, and the unique features of anesthesia practice that may contribute to such errors, there is a relative paucity of literature focused on preventable anesthesia medication errors. A recently published literature review of anesthesia drug administration errors over a 60-year time period cited 14 articles and 3 symposium reviews, and only 5 articles that explicitly address medication error rates during the conduct of anesthesia. [9] The reported frequencies of anesthesia medication error rates range from 1:133 to 1:450 cases, [10] [11] [12] [13] and these rates are based on provider self-reported errors. Additionally, these data are mainly from non-U.S., single or double-center studies, and National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) standardized definitions were not used for categorizing medication error severity.

With respect to the clinical and economic consequences of anesthesia related medication errors, the literature is even more sparse. One published review of the ASA Closed Claims Project database found that 4% of the cases were related to drug administration error, and these cases were associated with a 24% mortality and 34% morbidity, with an estimated annual cost of $2.8 million for a 700 bed hospital. [14] MEDMARX data report, which is generated from a database of 422 voluntary participating healthcare systems, is a commonly used reporting system for medication errors. [3] While these data are inclusive of the perioperative setting, and adhere to NCC MERP definitions for type and severity of medication errors, there is no resource utilization or cost data provided. Additionally, the participating health systems are predominantly <200 bed community hospitals. [9] One study found a two-fold increase in anesthesia medication errors by providers in-training versus in-practice. [15] Given this finding, it is important to investigate the anesthesia medication error rates and consequences at large academic hospitals, where providers-in-training are concentrated.

This study seeks to identify the incidence of perioperative medication errors, establish the severity of medication errors based on NCC MERP standardized definitions, and quantify the additional resource requirement associated with these errors.

Methods:

The study design is that of a retrospective incident record and medical record review with a nested case-control component. First, we propose a retrospective review and analysis of self-reported incident data (QA data). Perioperative medication errors and near misses will be identified in the QA data from the time period 2008 (or from the earliest date that each center began participation with MPOG) - present. This review will take place at individual participating sites and the de-identified medication error cases will be extracted to MPOG. Medication error cases which can be linked to existing, de-identified cases in the MPOG database will be included in this study. The following hospitals within the Multicenter Perioperative Outcomes Group (MPOG) expressed interest in participating: University of Michigan, Cornell University, Vanderbilt University, University Medical Center Utrecht, University of Colorado, Oregon Health Sciences University, Columbia University, University of Tennessee, Washington University, University of Vermont, University of Amsterdam, and Yale University. Funding will be available for up to 8 domestic participating sites.

One aim of this study is to characterize the epidemiology of perioperative medication errors. To do so, the existing MPOG data set, which includes comprehensive patient demographic, comorbidity, and intraoperative data, will be augmented at each site by a focused physician review of enterprise-wide, electronic medical record (EMR) data. Appendix III represents the data sheet each primary physician reviewer will complete for the validated medication error cases included in this study, and includes the following epidemiologic data: name, class and route of medication, NCC MERP classification of error severity (appendix I-II), and taxonomy, setting of error, category of facility, surgical service line, level of anesthesia provider involved, and where the implicated medication was compounded/prepared and labeled. Additionally, the

following resource utilization and patient outcome data pertaining to the medication error will be recorded: unplanned admission or escalation in level of care, need for invasive monitoring, cancellation or abortion of case, re-intubation, postoperative mechanical ventilation, and discharge disposition. Site reviewers will require access to the anesthetic record, admission history and physical, postoperative day 1-2 progress notes, and discharge summary to complete the required fields in the data sheet. At each site, a second physician reviewer will independently classify the NCC MERP level of severity and type of error (appendix III data sheet fields denoted with *). If there is a discrepancy in NCC MERP classification between the primary and secondary reviewers, or a difficult case to classify, a third reviewer will be required to adjudicate.

For the assessment of incremental differences in outcomes and resource consumption, this study will also entail matching incident cases with control cases without a reported error. Matching will be carried out only for those medication errors that were categorized as D-I using the NCC MERP Index (Appendix I), and where admission date is the same as the surgery date. We will match on the following variables: institution (same), type of case (exact anesthesia CPT code), date of case (+/- 1 year), ASA status (exact), emergent status and surgeon. If no matches are available, we will remove surgeon from matching criteria. Potential outliers for both error cases and control cases will be examined using Studentized residuals. If multiple matches are available, we will match up to 2:1 to, selecting the 2 cases in closest temporal proximity to the medication error case.

To help determine the incremental resource utilization associated with medication errors, for error cases and matched control cases (described above), we will query institution specific billing

data. Each participating institution will query and extract billing data (list charges) for medication error cases and case control patients. Specific methodology for this may include accessing UBO4 forms for error and control cases (to be determined). If possible, total charges as well as charge by category (e.g. routine days, intensive care days, pharmacy, radiology, supplies & equipment, operating room, anesthesia, other services,) will be captured. Using institution-specific cost-to-charge-ratios (CCR) published by the Centers for Medicare and Medicaid (CMS), billing data will be used to generate an estimate for cost of care.

Study Population

Medication errors will be queried from the QA incident reports transmitted to the MPOG central database by participating sites. All data from 2007 to current for which the participating site has valid and accurate QA incident data will be queried and analyzed.

Inclusion criteria

Incident cases that describe medication errors in an adult patient population undergoing anesthesia care between the "anesthesia start" and "anesthesia end" time points, as documented in the anesthetic record. The following care settings will be targeted for inclusion in this study: preoperative holding area, operating room, offsite locations for anesthesia care, post anesthesia care unit, labor and delivery wards, and inpatient transport under anesthesia care. Both inpatient and outpatient settings will be included.

Exclusion criteria

Pediatric cases (<18 years of age), and any medication errors that occurred outside of the "anesthesia start" to "anesthesia end" timeframe, as documented in the anesthesia record.

Study Procedures

Institutional Review Board (IRB) approval will be obtained by each site for this retrospective QA incident review. In addition, the University of Michigan will serve as the coordinating center and aggregate all the data into a limited dataset. All data transmitted to MPOG will be de-identified (except date of service) at the participating site prior to transmission and assigned a random de-identified code for which only the participating sites honest broker will have access to the patient's identifiers. Perioperative medication errors will be identified in the available QA incident reporting data and the de-identified code will be transmitted back to site for manual review. At each site, the honest broker will re-identify the patient for manual review of the event by at least two clinicians to classify the severity of the outcome using the NCC MERP classification framework. If there is a disagreement between the reviewers or a difficult case to classify, a third clinician will review the case for adjudication.

Safety and Efficacy or Effectiveness Endpoints

Main endpoints of interest are:

- Perioperative medication error epidemiology: incidence (lower bound based on self-reported data), relative frequency by type (NCC MERP classification), medications/class involved, provider, patient, service line characteristics.
- Difference in patient discharge disposition, clinical outcomes and healthcare resource use among those with errors and those without errors.

Statistical Rationale and Analysis Plan

All data processing and statistical analyses will be performed using SPSS® Version 22 (International Business Machine Corporation, Yonkers, New York) and SAS 9.3 (SAS Institute, Cary, North Carolina).

Overall incidence of self-reported perioperative medication errors will be determined. Annual incident rates will be assessed in aggregate and at the institutional level. Univariate descriptive statistics (frequencies and percentages) will classify medication errors based on information gathered from the data collection form:

Error-specific characteristics - individual medications, medication classes, severity of the error (based on NCC MERP category), types of error (based on NCC MERP category), setting of error, route of administration and make/labeling of the medication

Hospital/provider characteristics – surgical service line, type of facility and level of provider present during error

Patient outcomes - unplanned admissions, invasive monitoring, cancelled/aborted case, re-intubation, mechanical ventilation, and discharge disposition

Matched cases and controls will be compared to determine associations between patient outcomes (stated above) with medication errors. For categorical measures of patient outcomes captured in the data collection form, conditional logistic regression will determine significant differences between cases and controls. For continuous measures of hospital charges and category specific hospital charges, a Wilcoxon signed rank test will assess differences. Outliers will be examined using the Studentized residuals for continuous measures; a sensitivity analysis will be completed with outliers removed. Standard errors, in addition to 95% confidence intervals, will be reported.

References

1. *To Err Is Human: Building a Safer Health System,* ed. L.T. Kohn, J.M. Corrigan, and M.S. Donaldson. 2000: The National Academies Press.
2. Keers, R.N. et al., *Prevalence and Nature of Medication Administration Errors in Health Care Settings: A Systematic Review of Direct Observational Evidence.* Ann Pharmacother, 2013. **47:** p. 237-56.
3. Hicks, R.W., et al., 2006 MEDMARX data report: a chartbook of medication error findings from the perioperative settings from 1998-2005. USP Center for the Advancement of Patient SAfety 2006; Rockville, MD.
4. Gordon, P.C., R.L. Llewellyn, and M.F. James, *Drug administration errors by South African anaesthetists--a survey.* S Afr Med J, 2006. **96**(7): p. 630-2.
5. Labuschagne, M., et al., *Errors in drug administration by anaesthetists in public hospitals in the Free State.* S Afr Med J, 2011. **101**(5): p. 324-7.
6. Orser, B.A., R.J. Chen, and D.A. Yee, *Medication errors in anesthetic practice: a survey of 687 practitioners.* Can J Anaesth, 2001. **48**(2): p. 139-46.
7. Perel, A., et al., *Anaesthesiologists' views on the need for point-of-care information system in the operating room: a survey of the European Society of Anaesthesiologists.* Eur J Anaesthesiol, 2004. **21**(11): p. 898-901.
8. White, S.M., N. Deacy, and S. Sudan, *Trainee anaesthetists' attitudes to error, safety and the law.* Eur J Anaesthesiol, 2009. **26**(6): p. 463-8.
9. Cooper, L., et al., *medication errors in anesthesia: a review.* Int Anesthesiol Clin, 2013. **51**(1): p. 1-12.
10. Cooper, L., et al., *Influences observed on incidence and reporting of medication errors in anesthesia.* Can J Anaesth, 2012. **59**(6): p. 562-70.

11. Llewellyn, R.L., et al., *Drug administration errors: a prospective survey from three South African teaching hospitals.* Anaesth Intensive Care, 2009. **37**(1): p. 93-8.

12. Webster, C.S., et al., *The frequency and nature of drug administration error during anaesthesia.* Anaesth Intensive Care, 2001. **29**(5): p. 494-500.

13. Yamamoto, M., S. Ishikawa, and K. Makita, *Medication errors in anesthesia: an 8-year retrospective analysis at an urban university hospital.* J Anesth, 2008. **22**(3): p. 248-52.

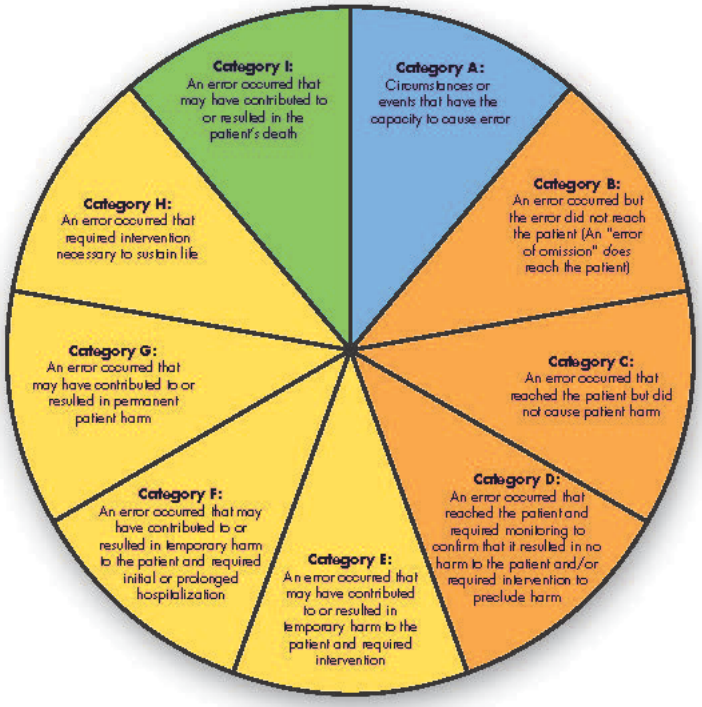
14. Bowdle, T.A., et al., *Drug administration errors from the ASA closed claims project.* ASA Newsletter, 2003. **67**(6): 11-13.

15. Cooper, L., et al., *Influences observed on incidence and reporting of medication errors in anesthesia.* Can J Anesth, 2012. **59**: 562-570.

16. Bates, D.W., et al., *The Costs of Adverse Drug Events in Hospitalized Patients.* JAMA, 1997. **277**: 307-311.

Appendix 1: NCC MERP Index for Categorizing Medication Errors

NCC MERP Index for Categorizing Medication Errors



Definitions

Harm
Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

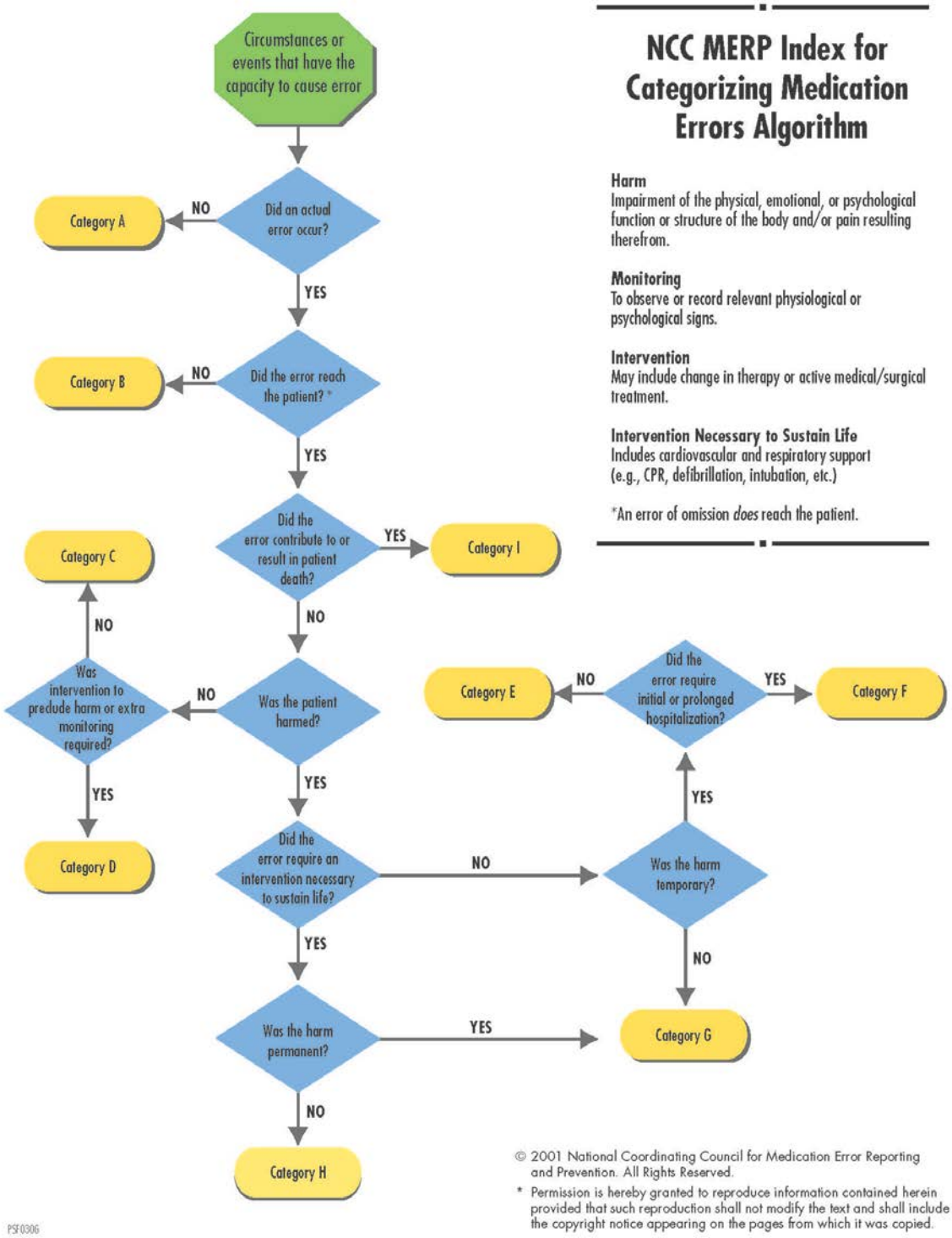
Monitoring
To observe or record relevant physiological or psychological signs.

Intervention
May include change in therapy or active medical/surgical treatment.

Intervention Necessary to Sustain Life
Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation, etc.)

PSR0306

Appendix II: NCC MERP Index for Categorizing Medication Errors Algorithm



The Epidemiology and Impact of Medication Errors in the Perioperative Setting

Data Collection Elements

MPOG De-identified ID:_____

I. The following data to be retrieved from the anesthetic record and QA/medication error report

1) Name of Medication: (drop down menu)_____

2) Class of Medication:

Antibiotic	IV anesthetic (Propofol, Etomidate, etc)	Succinylcholine
anticholinergic	Cardiovascular (ionotrope/vasopressor/vasodilator/beta-blocker/etc.)	Inhaled anesthetic
Anti-emetic	Local Anesthetic	Acetylcholinesterase-inhibitor
Benzodiazepine	Nondepolarizing NMB	Non-opioid analgesics
Coagulation Management (heparin, protamine, antifibrinolytics)	Opioid Analgesics	Other

****3) Type of error bases on NCC MERP taxonomy (please select all that apply):***

Dose omission	Improper dose	Wrong strength/concentration
Wrong drug	Wrong dosage form	Wrong technique
Wrong route	Wrong rate	Wrong duration
Wrong time	Wrong patient	Monitoring error[1]
Deteriorated drug	Other	

1 Examples include: drug-drug interaction, documented allergy, drug-disease interaction, drug-nutrient interaction, clinically inappropriate

4) Setting of Error:

Preoperative holding Surgical Operating Room Offsite anesthesia location (e.g. EP, IR, MPU, etc.) PACU During patient transport Other

5) Route of Medication Administration (intended):

IV push bolus[1] IV bolus drip[2] IV Infusion (set rate)[3] Enteric Inhaled
Subcutaneous Neuraxial Topical Per rectum Intraocular Other

1 Medication injected via syringe "push"

2 Medication hung as a bolus infusion

3 IV infusion medication delivered at a programmable rate

6) Level of provider present at time error occurred (if supervision model indicate the level of provider being supervised):

CA-1 CA-2 CA-3 Resident (unknown level) Fellow CRNA Attending
Other/unsure

7) How was medication made/labeled:

Compounded/labeled by pharmacy (e.g. pre-made, pre-labeled syringe)

Compounded/reconstituted/labeled by anesthesia provider Unsure

8) Did medication error result in or contribute to patient death while under anesthesia care?

Yes No

9) Did medication error result in or contribute to patient death within 30 days?

Yes No

10) Did medication error result in need for invasive monitor placement while patient under anesthesia care? (select all that apply):

Yes CV catheter Yes a-line Yes PA catheter No Unsure

11) Case cancelled or aborted as a result of medication error:

Yes No Unsure

12) If yes to above, was surgery performed/completed during the same hospitalization, or was the patient discharged to return at a later time?

Procedure completed same hospitalization

Patient discharged, returned at a later time for procedure

13) Patient re-intubated while under anesthesia care as a result of the medication error:

Yes No Unsure

II. The following fields to be informed through anesthetic record, admission H&P, POD 1-2 progress notes, and discharge summary

1) Date of case in which medication error occurred

(month/date/year)

2) Date in which patient was admitted to hospital

(month/date/year) patient not admitted (outpatient procedure/surgery)

3) Date of discharge from hospital (acute care setting)

(Month/date/year) patient was not admitted Patient did not survive to discharge

****4) Severity of Error via NCC MERP Category[1]:***

1 See appendix II for severity category flow-chart

A B C D E F G H I

5) Did medication error require an unplanned admission (for outpatient surgery):

Yes to floor Yes to moderate care Yes to ICU No Unsure

6) Did medication error require escalation of level of care for planned admission (inpatient operation):

Yes to moderate care Yes to ICU No Unsure

7) Mechanical ventilation in PACU resulting from medication error?

Yes No Unsure

8) Mechanical ventilation after discharge from PACU resulting from medication error:

Yes (<24 hours duration) Yes (>24 hours duration) No Unsure

9) Discharge disposition:

Alive to home Alive to skilled nursing facility/acute rehab/subacute rehab

Death Unknown

Appendix IV: **Process Diagram for Data Collection and Analysis**

Each **site** completes necessary regulatory paperwork	• IRB Approval (send approval letter to S. Housey) • Data use agreement (DUA) if necessary
Each **site** identifies necessary research personnel	• Financial Contact (send contact information to S. Housey) • 3 On-site reviewers (roles may be spit) • QA data colleagues • Billing data colleagues
Each **site** queries self-reported QA data for potential medication error cases	• We provided an example query in our last communication (keyword search), but each site will need to revise accordingly • Site champion with QA colleagues to perform initial screen for med error cases (pre-review)
On-site programmer links medication error cases to existing MPOG cases and flags with new MPOG Concept ID	• Concept ID = XXXXX • We can only accept cases linked to existing MPOG Case IDs, so please have current data uploaded into MPOG • US sites will receive initial funding installment ($7500)
Central MPOG programmer uploads cases into MPOG application suite and returns to the respective sites for manual review	• Data collection form will be electronic within the MPOG application suite • Reviewers will receive specific instructions for data collection
Physician reviewers complete electronic data sheets for medication error cases and de-identified data is transmitted back to MPOG central	• Reviewer 1 completes all fields, Reviewer 2 completes subset (*), Reviewer 3 adjudicates any discrepancies for subset (*) fields • Any combination of Reviewers 1 & 2 may be used; Reviewer 3 (site champion) should be consistent across all cases • Reviewers will need access to MPOG applicaiton suite, QA data report, electronic medical chart during manual review

Central MPOG progammer generates institution-specific case-control matches for medication error cases with NCC MERP class D severity or higher; deidentified cases and controls will be returned to respective sites.	• Only US sites continue with case-control matches and billing data • Matching criteria: institution (same), type of case (exact anesthesia CPT code), date of case (+/- 6 months), ASA status (exact), and surgeon. If no matches are available, we will remove surgeon from matching criteria. • If possible, 2:1 match
On-site programmers query and process patient charge data for cases and controls from billing department and upload into existing MPOG system	• We will provide more detail regarding what charges to capture
Central MPOG programmer cleans and processes charge data	• Total charges as well as charge by category (ICU bed, general care bed, pharmacy, radiology, laboratory) will be compared between the medication error and case control groups • Cost conclusions will be inferred from charge (billing) data
Biostatistican analyzes data per study protocol	• Overall incidence of self-reported perioperative medication errors will be determined (assessed at aggregate level) • Univariate descriptive statistics will classify medication errors (taxonomy, severity, and patient impact) • Matched cases and controls will be compared to estimate cost of perioperative medication errors
Study investigators prepare deliverables - manuscript sent to client and to high-impact journal	• US sites will receive second funding installment ($7500)