Part B: Experimental Design and Protocol
Human Subjects Protocol Application:

Title: Evaluation of Outcomes in the Post Anesthesia Care Unit

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Please provide a brief summary or abstract of this research protocol.

Quality outcomes in the Post Anesthesia Care Unit (PACU) have always been a goal of hospital care at Boston Childrenôs Hospital (BCH). A considerable number of metrics can be used to measure quality of outcomes in the PACU - such as the incidence of postoperative pain, the incidence and degree of emergence delirium, and number of patients who experience post-operative vomiting. The purpose of this study is to evaluate the quality of outcomes in the PACU at BCH and to identify preoperative demographic and behavioral data as well as intraoperative and anesthetic predictors of adverse PACU outcomes. We believe this will help us improve post anesthetic care quality and create a higher level of satisfaction for patients, family, and health care providers.

1. Specific Aims /Objectives

Specific Aim 1: Evaluate the quality PACU outcomes at BCH in term of the incidence of postoperative pain, emergence delirium and vomiting.
Specific Aim 2: Identify preoperative and intraoperative predictors associated with adverse PACU outcomes *e.g.* pain, emergence delirium, and vomiting. We will also investigate the impact of care on post-hospitalization behavioral changes and satisfaction of patients and families with perioperative care.

2. Backgrounds and Significance

High quality outcomes in the Post Anesthesia Care Unit (PACU) bears greatly on the quality of care provided in the perioperative timeframe at Boston Childrenôs Hospital (BCH). High quality PACU outcomes decrease the total workload for PACU nurses, decrease the chance of injury to patients, and increase satisfaction of patients, families, and care-givers. In addition, it is possible that PACU outcomes have an impact on longer term behavioral, emotional, and satisfaction outcomes for patients and families. We propose a multidimensional study that will specifically evaluate the quality of outcomes in the BCH PACU with a multidimensional approach. We will begin by codifying the nature of the emergence behaviors and side effects that occur in our PACU. We will then evaluate specific elements of the preoperative assessment (developmental status, behavioral issues, etc.) as well as the operative care of patients, and evaluate if pre-existing personality issues or specific aspects of care in the operating room correlate with the nature of the recovery in the BCH PACU. We will also evaluate the patient behavior (per parent report) or stress (per youth report) two days and two weeks after the procedure to determine if there are any persistent (2 days or 2 weeks) behavior changes

after the procedure. Ultimately we will investigate whether or not any elements of the pre-operative evaluation or operative care impact these late behaviors.

It is hoped that by looking at our primary outcomes ï that of pain, emergence delirium, and vomiting in the PACU ï with respect to patient factors and anesthetic management we will identify patients who are at particularly high risk for adverse PACU outcomes as well as anesthetic techniques that are associated with optimal PACU outcomes.

Finally, we will ask both the PACU nursing staff and a subset of 35 parent participants individually and anonymously to rank our primary outcomes by level of relative importance among the various phenomena that occur during emergence from anesthesia that we are documenting. We will ask the PACU nursing staff to rate the importance of each of these issues based on her or his experience as to how much they impact the well-being of a child as she/he wakes up from anesthesia. We will ask parent participants to provide their opinion of the relative importance of each factor to their childôs recovery in the PACU. These participants will be asked to rate the importance of each of the issues as to how much they feel they may impact the well-being of their child as s/he wakes up from anesthesia. This information will be combined with the risk data to develop risk models for adverse PACU outcomes that are based on both the study data and expert opinion from the PACU and families. This rating sheet for nurses is attached to the online study submission as the ñEmergence Questionnaire for PACU Nurses.ò This rating sheet for parent participants is attached to the online study submission as the ñEmergence Questionnaire for Families.ò

3. Preliminary Studies/Progress Report

A recent audit of pain in the PACU setting at BCH was completed by PACU medical director Richard Blum MD and members of the PACU nursing staff. The audit was completed over 2 days involving all patients that received care in the PACU. The maximum pain score within one hour of arrival was recorded using FLACC, Wong Baker Faces Score, or visual analog scale (numerical scale). The results showed that 30% of patients had a pain score of 5 or greater on a 10 point scale and 9% recording 7 or greater on a 10 point scale.

4. Design and Methods

a. Study Design

This will be a prospective observational study that will follow patients on the day of surgery from arrival in the Day Surgery Unit or Preoperative Holding Unit, into surgery, and through their recovery in the PACU. Subsequently we will evaluate post-hospitalization behavior changes at 2 days and 2 weeks after the surgery.

b. Patient Selection and Inclusion/Exclusion Criteria

We will enroll all patients ages 6 months to 30 years undergoing the following qualifying surgeries:

- **Genito-Urinary/Urology Department**

  Circumcision, Orchidopexy, Hypospadias Repair, Hernia Repair, Cystoscopy, Pyeloplasty, and Ureteral Reimplants or Ureteral Stents

- **Otolaryngology Department**

  Tonsil and/or Adenoid Removal, Tympanostomy, Tympanoplasty, and Mastoidectomy

- **Orthopaedics Department**

  Hip and Knee Arthroscopies, Hardware Removal, and Tendon Lengthening

- **Plastic Surgery Department**

  Alveolar Cleft Repair

Enrollment will include those patients identified in their Pre-Anesthesia Record as having developmental delay or decisional impairment. Also included in enrollment will be those patients having these qualifying surgeries performed together with the following procedures typically co-occurring with them: laryngoscopy or bronchoscopy (for the tonsillectomy/adenoidectomy or adenoidectomy only patients) and inguinal herniorrhaphy or excision of appendix epididymis (for the circumcision or orchidopexy patients). Selection of patients ages 6 months to 21 will continue to occur for all qualifying surgeries except for those patients scheduled for hip arthroscopy. A majority of these hip patients are over 21 years. By expanding the eligible age range for just this subset of qualifying patients to 30 years, we seek to insure collection of enough information on this subset to allow for effective comparisons with all of the other outcomes data collected from participants scheduled for the other qualifying surgeries.

These qualifying surgeries are performed on approximately 40 patients per week. Patients having these procedures have been identified as having high rates of pain and emergence delirium postoperatively by the PACU nursing staff. In addition, review of anesthetic records reveals that there is significant variability in the nature of the general anesthesia, regional/local anesthetic, and adjunctive medications (ondansetron, decadron, acetaminophen, NSAIDS) used in the perioperative period for these patients. For example, there is approximately 20% use of some form of continuous intravenous anesthesia vs. inhaled anesthesia. Additionally there is variation in the use of peripheral nerve blocks vs. local infiltration, vs. systemic opiates as the primary analgesia for many of these procedures when performed in older patients in our population.

c. Recruitment Methods

We plan to offer participation to all patients ages 6 months to 30 years who are scheduled for circumcision, tonsillectomy/adenoidectomy, adenoidectomy only, hip or knee arthroscopies, orchidopexy, tympanoplasty or tympanotomy, and hypospadias repair surgery at Boston Childrenôs Hospital Longwood Campus. We will recruit through the surgical sections that are performing these surgeries by alerting all patients of the presence of the study at the time they are scheduled for the surgery ï by their surgeon. Families will be given a brochure describing our methodologies in lay language at the time of their appointment with their surgeon. If the brochure is not obtained at the time

of the surgical visit, it will be sent by mail 1 week prior to their preoperative clinic visit or scheduled surgery (if no preoperative visit is planned). This brochure will include a link to a web-based, informational study video. Potential participating families will be encouraged to view the video. Prior to the preoperative clinic visit or scheduled surgery, we will contact each potential participant by telephone to gauge their interest in participation and answer any questions concerning participation and/or the informational video. If the family agrees to participate a written consent form will be provided in the Preoperative Clinic or in the Day Surgery Unit (if no preoperative visit is scheduled).

The ñEmergence Questionnaire for PACU Nursesò will be provided anonymously and confidentially to all PACU nurses for one-time completion.

We anticipate approaching up to 60 participating families across the range of nine qualifying surgeries (excluding hypospadias repair) about completing the Emergence Questionnaire for Families, to obtain 35 completed surveys. For the most part, patients scheduled for hypospadias repair are too young to participate in this study. At least three families from the other eight qualifying surgeries will be approached, with selection for participation occurring in the order these families are scheduled for surgery once Committee approval is obtained. Completing the survey should take an additional five minutes per family and will be done confidentially and anonymously after Consent/Assent is obtained together with the psychology questionnaire.

d. Description of Study Treatments or Exposures/Predictors

- Preoperative (Remote): We will identify potential participants from preoperative scheduling data available through the various surgical sections we will be working with for this study. Description of the study will be given to families at the time of their appointment with their surgeon when surgery is planned. If the description is not obtained at the time of the surgical visit, it will be sent by mail 1 week prior to their preoperative clinic visit or scheduled surgery (if no preoperative visit is planned). These materials will include an electronic link to a study-specific video designed to answer specific questions regarding risk, benefit, design, enrollment, etc. On a day before preoperative clinic visit or scheduled surgery, we will contact each potential participant by phone to gauge their interest in participation and answer any questions that exist concerning participation. If the family agrees to participate in this study, a written consent form will be provided in the Preoperative Clinic or in the Day Surgery Unit (if no preoperative visit is scheduled).

- Preoperative (Day of Surgery - Demographics): Demographic data on each patient will be collected ï including age, weight, diagnosis, history of previous surgery (yes/no), coexisting major medical problems, developmental status, and any psychological diagnoses such as autism or oppositional behavioral problems that require medication or alternative school/day care arrangements. This data will be obtained from the electronic medical record after enrollment in the study on the day of surgery or in the preoperative clinic. Additional demographics, collected via parent self-report, will include parent(s) marital status, occupation, and education. This information is routinely collected in pediatric psychology research to effectively characterize participating familiesôsocial and economic status (SES). For those patients ten years of age and older

who are undergoing either knee or hip arthroscopy, we will ask for an average pain score in the past two to three weeks as well as whether any pain medication is being taken.

- Preoperative (Day of Surgery ï Psychological Profile): On the day of surgery we will collect a behavioral inventory on each child without developmental delay or decisional impairment that allows us to understand his/her developmental status and aspects of their emotionality andsociability. This will consist of a short survey of questions.The short survey will be age specific. The surveys to be used for this study are presented in Appendix 1, and include specific versions of child-normed, youth-normed, and an adult-normed temperament questionnaire developed specifically for recruitment of all patients ages 16 years and above through the age of 30 years. The already-approved Childrenôs Behavior Questionnaire will be administered to parents with children ages 3 ï 6. The already-approved Temperament in Middle Child Questionnaire will be administered to parents with children ages 7- 9. The Early Adolescent Temperament Questionnaire , revised to include an additional nine questions accidentally omitted from the currently administed EATQ, will be administered directly to youth ages 10 ï 15. We also will assess aspects of emotionality more broadly, specifically through use of the observational Yale Pre-Operative Anxiety Scale (YPAS-m). This observational scale is one that the research coordinator will complete (i.e., it is not a self-report questionnaire that must be administered to patients or families) and has been validated for our proposed use with patients ages 2-12 to further assess pre-operative behaviors of interest for characterizing emotionality.

The Adult Behavior Questionnaire will be administered directly to youth ages 16 ï 30. Study staff have determined from administration from August, 2013 ï November, 2013 of only the PHBQ to all enrolled families, irrespective of participant age, that the PHBQ is not an effective measure of post-operative behavior in older children and adults. Substantial family feedback indicates the questions about changes in behavior post-operatively on the PHBQ are geared primarily to young or middle aged children, ages 2-12. Adding the CPSS to the studyôs postoperative battery for administration to youth and adults ages 13 ï 30 is expected to address this deficiency effectively, thereby facilitating collection of more complete information about post-hospitalization behavioral changes from all youth enrolled in the study.

These surveys will not be administered to those children or legal guardians overseeing the care of children with developmental delay or decisional impairment.

- Preoperative (Day of Surgery ï Induction): Data on the nature of the induction of anesthesia will be collected using the Induction Compliance Checklist (ICC). (Appendix 2.)

- Intraoperative: Data on the intraoperative care of each patient will be collected through the Automated Information System (AIMS) at Boston Childrenôs Hospital. The information will include type of regional anesthesia (epidural anesthesia or peripheral nerve block), use of local anesthetic for wound infiltration, use of inhalation agent (type and MAC level), propofol infusion (both as sole anesthetic agent and as adjunct to

general anesthesia), dexmedetomidine (bolus or infusion), dexamethasone (dose), and ondansetron (dose).

- Postoperative (PACU Data): In the PACU recovery data on each patient will include:

1. Pain behavior information using the FLACC scale (Appendix 3.) or Wong-Baker Faces Scale (Appendix 4) for patients 7 years old and younger. A visual analog scale (VAS) (Appendix 5.) or numerical pain scale (NPS) (Appendix 6.) will be used for developmentally appropriate older patients. An adapted Numerical Rating Scale that is used already in the PACU to characterize pain in developmentally delayed or decisionally impaired patients will be used for these participants.
2. Emergence agitation categorization through use of the Pediatric Anesthesia Emergence Delirium Scale (PAED) (Appendix 7.).
3. Episodes of emesis will be recorded along with the total time the child spent in the PACU.

These measures will be recorded by reporting the highest level of pain or agitation that occurred for every 15 minute interval. In addition, any time vomiting occurs ï it will be recorded.

- Postoperative (Remote): The behavior of patients ages 2 - 12 will be assessed using the Post-Hospitalization Behavior Questionnaire (PHBQ) (Appendix 8). The behavior of youth and adults ages 13 ï 30 will be assessed using the Child PTSD Symptom Scale (CPSS). Each family will be given 2 copies of the age-specific questionnaire at the time of surgery along with an instruction sheet concerning when the questionnaire should be completed. A self-addressed, stamped envelope will be included. Families will be called to remind them to complete the questionnaire if we have not received it within 2.5 weeks after discharge. They will be given the option to complete the questionnaire by phone. A clinical psychologist will review CPSS responses upon receipt and arrange with a parent or the patient (for participants over age 18) for a discussion of treatment recommendations in the event that significant post-operative stress is reported. Given the timeframe for the development of post-operative stress, we believe the 2-week window should suffice as a sufficient follow-up time for evaluation and the provision, potentially, of referrals for further evaluation or treatment.

- Postoperative (Remote): At the same time we collect the PHBQ data, we will question the family on their satisfaction with the perioperative care of their child (for those under 13). For patients over 11, we will ask for their satisfaction with the perioperative care they received. This will be done using three questions designed to elicit (1) satisfaction with recovery in the PACU; (2) global satisfaction with the surgical care at Boston Childrenôs Hospital; and (3) indication of whether healthcare had to be sought at Boston Childrenôs Hospital or another health facility as a result of the surgical services provided. Answers to the first two questions will be solicited on a simple scale from 0 to 10 with 0 being óvery badô and 10 being óexcellentô. The third question is worded yes/no, and participants also will have the opportunity to explain qualitatively why they have answered either yes or no.

A member of the study team will mail a follow-up thank-you postcard to all those participating families for whom all follow-up documentation has been completed and mailed to/received back at Boston Childrenôs Hospital within two weeks of receiving completed follow-up materials.

e. Definition of Primary and Secondary Outcomes/Endpoints

Primary outcomes:

1. Incidence of significant pain defined by pain behavior information from FLACC scale, Wong-Baker Faces scale, visual analog scale/numerical scale or adapted numerical rating scale ï equal to or more than 5 on a scale from 0 to 10 at any time during the PACU stay.
2. Incidence of agitation using emergence agitation categorization with PAED scale equal to or more than 10 on this scale for more than 30 seconds during the recovery period.
3. Post-operative vomiting (POV) will be measured by episodes of vomiting or retching in PACU. This will be a binary outcome ï either vomiting/retching occurred or it did not.

Secondary outcomes:

1. Satisfaction of patients and families with perioperative care, as determined from a three-question satisfaction survey allowing participating families to rate their recovery experience, global surgical experience, and need for further care at another healthcare facility.
2. Post-hospitalization behaviors changes defined by development of 4 or more behavior changes on the Post Hospitalization Behavior Questionnaire (PHBQ) or development of increased stress levels on the Child PTSD Symptom Scale (CPSS).

5. **Data Management and Statistical Analysis**

a. Data Management Methods

Data will be collected from several sources:

1. Questionnaire data from the personality profiles performed in the preoperative venue will be entered into a computer database by the study coordinator.
2. Data on induction compliance will be collected on a paper record and then transferred to a database by the research coordinator.
3. Data on demographics for each patient will be obtained from a review of the CHAMPS data on each patient and entered into the study database.
4. Data on specific parameters of the intraoperative management will be collected and stored in the AIMS data system.

5. Data concerning PACU outcomes will be collected on the electronic PACU flow sheet and entered directly into the study database.
6. Data from the PHBQ, CPSS, and Satisfaction surveys will be taken from paper record and recorded directly into the study database.

7. Data from the ñEmergence Questionnaire for PACU Nursesò will be taken from paper record and recorded directly into the study database.

b. Quality Control Method

Data will be verified by investigators after being loaded into the database.

c. Data Analysis Plan

- Raw data on the number of children who emerge from anesthesia with severe pain as per FLACC/Faces readings, VAS/NRS or adapted NRS will be recorded.
- The number of children who experience Emergence Delirium defined as a PAED score of 10 during their PACU stay ï will be recorded.
- The number of children who experience vomiting or retching without frank emesis will be recorded.
- Time required to meet PACU discharge criteria will be recorded.
-Outcomes will then be analyzed with respect to the pre-operative demographic and behavioral/psychological profiles that were collected on each patient with broad analysis categories created for patients with developmental delays (these subjects will provide only demographic data), autism (these subjects will provide only demographic data), high index for emotionalityor low sociability.
- Further analysis will evaluate the impact of anesthetic technique metrics on the duration of PACU stay, percentage of patients with pain scores reflecting severe acute pain in the PACU; PAED scored reflecting emergence agitation, and rates vomiting. Specifically, the use of regional anesthesia will be evaluated. The use of a propofol infusion during the anesthetic as well as the amount (and type) of opiate used during the case will be evaluated. The administration of adjunctive medications such as dexamethasone, ketorolac, acetaminophen, or ondansetron will also be evaluated. Logistical regression analysis will be used to determine if any of the above is independent predictors of poor perioperative outcomes. Data from the ñEmergence Questionnaire for PACU Nursesò will be combined with results from the logistical regression analysis to support the development of comprehensive risk models for predicting adverse PACU outcomes that are based on, or drawn from, both the study data and expert nursing opinion.

- Follow up data on behavioral outcomes will be obtained using the PHBQ and CPSS tools. The rate of 4 or more new behavioral changes on the PHBQ or the reporting of behavior indicative of post-operative stress will be evaluated with respect to patient demographic data (age, pre-existing diagnoses) and the data on primary outcomes during the PACU stay.

d. Statistical Power and Sample Considerations

This is an observational, longitudinal study. As such we are not performing a power analysis to determine required sample sizes. Given the current frequency of these surgeries we will enroll approximately 20-25 patients per week in this study. After 6 months we expect to have 600 patients in our database. The primary aim of this study is to use our specific metrics to determine the percentage of patients in our PACU who have one or more of our primary outcomes. We will also determine the percentage of patients who have behavior changes at 2 days and/or 2 weeks after the procedure (PHBQ measures) and the overall satisfaction with our perioperative care (families and patients) as determined by the satisfaction outcome scores.

Our secondary aim is to assess the relationships between various patient and procedural characteristics and primary PACU outcomes as well as the PHBQ outcomes. We will perform a univariate logistic regression analysis of potential predictor variables including patient psychological profiles, induction behaviors, and anesthetic management as well as the operative procedure itself. Using the results of this univariate analysis, we will develop multiple logistic regression models. Multiple logistic regression models will evaluated manually in a stepwise fashion to determine characteristics associated with primary and secondary outcomes. This information will be combined with data from the ñEmergence Questionnaire for PACU Nursesò so that the final models are based on both study outcome data and expert nursing opinion.

e. Study Organization

None

f. Data and Safety Monitoring Plan

All data that is to be released to investigators will be reviewed prior to release to ensure maintenance of confidentiality.

6. **Risk and Discomfort**

This is an observational study not involving greater than minimal risk. This research will not influence or change any treatment course.

7. Privacy Provisions

Patient privacy will always be respected in any study activity. For this study, this is limited to the process of behavioral evaluation in PACU and postoperative care unit.

8. Confidentiality Provisions

All paper records are kept in locked cabinet with access restricted to the investigators. The electronic registry data are restricted to separate, external drive disks which are accessed from a computer. Those drives, in turn, are accessed from a separate system configuration (partition) that has been established to further enhance security. The operator uses a distinct system configuration, one that only recognizes the high capacity disk drives, when he/she is using the database.

The computerôs hard drive and associated applications are not ñseenò or open on the computer during this time. In practical terms, this means that the operator cannot

accidentally access the Internet while working with the data. It also means that in the event that the computer is stolen, the data will not be found on the computer.

The Internet connection is on the computerôs hard drive. The operator uses another system configuration, one that only recognizes the hard drive, when he/she is using the Internet. A firewall program, Black Ice Defender, is used to prevent outsider intrusion into the computer itself during an Internet connection. An anti-virus program, Norton AntiVirus, prevents viruses from infecting the computer and is updated every time new definitions become available. Both products are upgraded when new versions are offered.

To further enhance security, the high capacity disk is backed up at least daily, and stored in a secure location, so that there are always two copies of the electronic records. One copy is kept on site and one off site. This also addresses the concern for avoiding damage due to catastrophes, such as fire. Use of the electronic data base and filing cabinet is limited, and is password protected. The computer itself is kept in a locked facility.