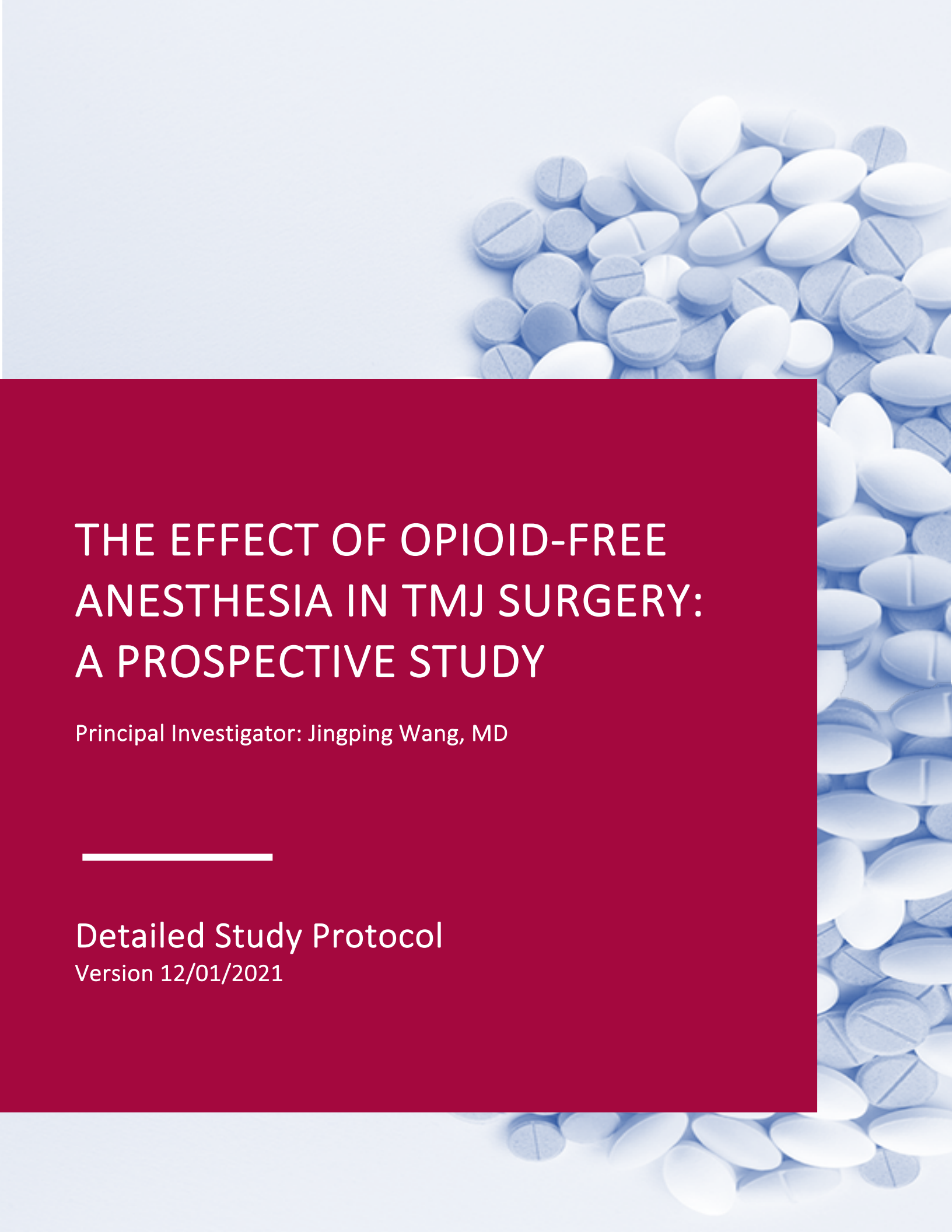

THE EFFECT OF OPIOID-FREE ANESTHESIA IN TMJ SURGERY: A PROSPECTIVE STUDY

Principal Investigator: Jingping Wang, MD

Detailed Study Protocol

Version 12/01/2021

Table of Contents

Background and Significance 3
Specific Aims 3
Subject Selection 3
Subject Recruitment 4
Consent Procedures 4
Randomization and Masking 5
Drug Administration 5
Study Procedures 5
Withdrawal or Early Termination of Study Procedures 6
Other Standards of Care 6
Study Endpoints and Outcomes 6
Sample Size Calculation 7
Statistical Analysis 7
Risks and Discomforts 7
Potential Benefits 8
Data Collection, Source Documents and Confidentiality 8

Background and Significance

The intensity of pain after OMF surgery is often underestimated, and inadequate pain control may be associated with poor quality of recovery, increased opioid requirement and increased hospital length of stay postoperatively.

This population of OMF surgery is also susceptible to opioid-induced complications such as respiratory depression and postoperative nausea and vomiting, and may benefit from opioid-free anesthetic techniques.

Opioid free anesthesia is a safer option for anesthesia administration that maximizes a patient's respiratory ability and aggressively treats their pain, while eliminating the unwanted side effects of opioids. Although subanesthetic infusions of lidocaine, ketamine or dexmedetomidine supplemented with other intravenous agents and inhaled anesthetic has been used widely in surgeries, it's effect in postoperative pain management and overall hospital course has not been systematically studied in OMF surgeries.

Specific Aims

This study aims is to evaluate the effect of opioid free total intravenous anesthesia on postoperative quality of recovery in patients undergoing oral and maxillofacial surgery (OMF) temporomandibular joint (TMJ) surgery.

We hypothesize that by using an opioid free anesthetic technique, we can reduce the patients' postoperative pain score, reduce the amount of time until the patient meets the criteria for discharge from PACU, and reduce postoperative opioid consumption while in the PACU and within the subsequent 24 hours with less side effect of opioid usage.

Subject Selection

This study will enroll 60 patients undergoing TMJ surgery at Massachusetts General Hospital. Specifically we aim to enroll patients undergoing arthroscopic surgical procedures. We will not exclude repeat surgeries, as the anticipated intraoperative medication use and postoperative course is believed to be similar to patients undergoing TMJ for the first time. Specific inclusion and exclusion criteria are detailed below:

Inclusion Criteria

- Patients aged 18 to 75 (*inclusive*)
- Scheduled for TMJ surgery (including both unilateral and bilateral procedures)
- Planned arthroscopic surgical procedure
- Preoperative plan to discharge the same day

Exclusion Criteria:

- Inability to provide written informed consent
- Pregnant patients
- Open TMJ Surgeries
- Planned overnight admission
- Mental status disorder or patient who are unable to communicate

We will enroll patients without regard to race, sex, or ethnicity.

Subject Recruitment

Prescreening will be accomplished by reviewing the operating room schedule and surgical consult lists for patients who are scheduled to undergo TMJ surgery. Patient medical records will be reviewed for inclusion and exclusion criteria. All patients meeting inclusion criteria with no exclusions will be considered eligible for participation and approached as outlined below.

This study will utilize multiple modalities to recruit potential patients. Whenever possible a member of the study team will meet the patient at a preoperative clinic visit. At this time the study procedures will be explained in detail. The subject will be provided with a copy of the consent form and the consent process may be initiated. The patient will be provided with ample time to consider study participation, and will be encouraged to discuss participation with their surgeon or family members prior to making a decision. Subjects who are contacted in person and require additional time to consider participation will be reapproached on the morning of surgery in the preoperative holding area.

In some cases however it is not possible to meet with patients in person prior to their scheduled surgery. This is increasingly common as telehealth is incorporated into the preoperative arena. For patients with whom we are unable to connect at their preoperative clinic visit, we will either contact them through Patient Gateway Targeted Research Announcements or mail them a recruitment letter (if they do not use Patient Gateway). Both methods of patient recruitment will have information that describes the study procedures and allows them to opt out of participating in the study. Importantly we will obtain approval from the patient's surgeon or primary care physician prior to contacting any participants.

The recruitment packet that will be mailed to participants includes a letter that is signed by both the principal investigator and the patients surgeon/PCP, as well as copy of the informed consent form. Participants who are not interested in participation will be provided with a phone number and email address that they can contact in order to opt out of participating. If a subject remains interested in participating, they will be approached in person or via phone by a physician member of the research team to conduct the full informed consent process. Importantly, subjects can decide to participate or not in this study at this time. By providing the consent form in advance of the preoperative visit, this provides subjects ample time to consider participation and ask any questions.

All patients will be reminded that participation is entirely voluntary and that their decision to participate will in no way affect the care that they receive.

Consent Procedures

Written informed consent will be obtained by one of the participating physician researchers of the study. At the time of consent, all study procedures will be explained in detail, including the associated risks and benefits. The subjects will have the opportunity to ask any and all questions, and will be reminded that participation is voluntarily. Subjects will be reminded that their decision to participate or not will in no way affect the care that they would otherwise receive as part of their surgery.

All subjects will be consented with curtains drawn or the door closed, assuring patient privacy. Written informed consent will then be obtained prior to surgery and initiation of any research procedures.

In addition to in-person consent, this study will also utilize a MGB REDCap eConsent. Participants who have not contacted the study team (to opt out) will be contacted via phone prior to surgery by one of the physician study team members. During this call the physician will describe all of the study procedures and ensure all of the patient's questions have been answered. If after this conversation, the patient agrees to participate, the study team will send them a link to the eConsent via email. The participant will then be able to review the consent form and sign to consent. The study physician will also receive a REDCap link to sign off on consent. A collated copy will be returned to the participant for their records. Patients who prefer to consent in person

or those who are unable to complete the eConsent will be approached in person on the morning of their surgery as detailed above.

Randomization and Masking

Patients who consent to participate will be randomized to one of two groups in a 1:1 fashion using permuted block randomization. The randomization schema will be developed by a statistician and displayed in the REDCap randomization module.

Because this study involves two distinctly different medication administration strategies in the operating room, it is not possible to blind the treating anesthesiologist. Therefore this study will not be blinded to the treating provider. The patient will remain blinded to their assigned randomization group in order to obtain unbiased assessments of pain and anesthesia outcomes postoperatively.

Drug Administration

Anesthetic care will be standardized according to current institutional standards of care. Intraoperative clinicians will not be blinded to group assignment. Patients will be randomized to one of two groups:

- *Group 1 – Opioid-free Anesthesia Patients:* Patients who are not receiving opioids but the total intravenous anesthetic during surgery.
    - Patients in this group will receive an infusion of lidocaine, ketamine, or dexmedetomidine supplemented with other intravenous analgesics and intravenous and inhaled anesthetics, as needed clinically This includes administration of 5 mcg/kg/min of ketamine plus 0.5 – 1.0 µg/kg/hr of dexmedetomidine (Precedex) as a continuous infusion, started from induction to stop one hour before surgery is anticipated to end.
    - The exposure group will not receive opioid analgesic during the intraoperative period.

- *Group 2 – Standard Anesthesia Patients:* Patients who undergo the standard of care and receive opioids as part of their anesthetic regimen.
    - In this group patients will receive fentanyl (1mcg/kg or equivalence dose) every 45 minutes until the end of surgery, or as needed clinically.

Both groups employ strategies that are routinely used as part of standard clinical practice for TMJ surgery. Patients will otherwise receive the institutional standards of care for their surgical procedure and perioperative care.

Study Procedures

Following intraoperative drug administration patients will be followed until discharge from the PACU to assess study endpoints while in the hospital. This includes a complete review of their medical record. Clinically documented pain scores will be abstracted from the medical record based off nursing documentation which routinely occurs every 15 minutes. Medication administration, particularly with respect to postoperative opioids, and anesthesia-related complication (postoperative nausea, vomiting, etc.) will be recorded.

At the time of discharge from the PACU, members of the study team will ask the patient to compete a brief survey on their satisfaction with pain management. This Revised American Pain Society Patient Outcome Questionnaire is a validated scale of 12 questions that takes approximately five minutes to complete.

Patients in this study will be anticipated to be discharged the same day as the surgical procedure. At the time of hospital or PACU discharge, the patient will be provided with a Medication Diary. This will be used to record pain medication administration in the first 48 hours after surgery, as well as any pain or

complication they might experience at home. This diary will help to avoid recall bias when reporting these to the study team. Patients will then be contacted by the study team after postoperative day two to collect the information from the medication diary. The patient will be asked to mail or email a completed copy of the Medication Diary to the study team, if possible. If these cannot be returned a complete record will be obtained verbally during the phone call. At this point the subjects participation will be considered complete.

Withdrawal or Early Termination of Study Procedures

Regardless of the randomization group patients are assigned to, the attending anesthesiologist has the discretion to treat any pain or discomfort, as needed clinically, as deemed appropriate. If subjects require additional pain medication dosing to achieve comfort, it will be provided to ensure adequate analgesia for both of groups. We will attempt to minimize crossover from the opioid-free group by standardizing the anesthetic regimen, as outlined above in the Drug Administration Section, while providing adjuvant non-opioid strategies first. This will not constitute termination of the study. If this is the case, these patients will be analyzed according to the intention-to-treat principle. Participants will be encouraged to complete the study, as planned, through postoperative day two.

As with any research study, participation is completely voluntary. At any time the patient can request to withdraw from the study and all study procedures will be stopped.

Other Standards of Care

Importantly, enrolled patients will undergo the current institutional standards of care for their surgery and preoperative care. This includes, following adequate oxygenation, propofol (2-2.5 mg/kg), succinylcholine (1 mg/kg) and lidocaine (IV 1-1.5mg/kg bolus) as part of induction, and patients receiving general anesthesia with nasal intubation.

All patients will take receive PO acetaminophen 950 mg before going to the operating room unless otherwise contraindicated. Anesthesia maintenance will be maintained using a sevoflurane concentration of 0.7-1.3 minimum alveolar concentration (MAC). Ketorolac (30 mg IV) will be administered at the end of the case at the clinician's discretion. Local multimodal anesthesia infiltration will be performed before closure by the surgeon for all cases per standard protocol. Multimodal anti-emetics including dexamethasone (12mg IV), ondansetron (2-4 mg IV), haloperidol (1mg IV) or Toradol (30mg IV) will be administered prior to emergence per standard protocol, unless otherwise contraindicated.

Patients will be discharged home the same day with the following standardized discharge medications for TMJ arthroscopic surgery (unless otherwise contraindicated): Percocet (5/325mg, PO Q6H PRN pain; disp: 20 tablets), Mobic (7.5mg PO Q daily; disp: 60 tablets), and Flexeril (5mg PO QHS; disp: 60 tablets).

Patients would receive the treatments above regardless of whether or not they decided to participate in the study.

Study Endpoints and Outcomes

Primary and secondary study endpoints include:

Primary Endpoint

1. Postoperative Pain Score*: Pain will be measured using the eleven point (0 to 10) numeric rating scale. Pain scores will be recorded every 15 minutes until discharge from the post-anesthesia care unit (PACU) and at 12 and 24 hours postoperatively. Clinically documented pain scores will be recorded. Our primary outcome will be the worst documented pain score while in the PACU. Additional pain score time points will be evaluated as secondary endpoints.*

Secondary Endpoints

2. Perioperative Opioid Use: *Intraoperative and postoperative opioid consumption in the first 12, 24 and 48 hours postoperatively will be evaluated.*
3. The use, dosage and time to use of rescue analgesia in the PACU
4. The incidence of postoperative nausea and vomiting in PACU and at home after surgery
5. Pain Satisfaction*: Self-report pain satisfaction will be assessed at the time of PACU discharge using the Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R).*
6. Incidence of Opioid Related Adverse Effects: *The incidence of ileus, nausea/vomiting, and pruritis will be reported.*
7. Length of PACU and Hospital Stay
8. Total dose of Percocet used at 24 and 48 hours after surgery

Sample Size Calculation

Using data from previous study (Ahiskalioglu et al. Multimodal Approach to Postoperative Pain. J Oral Maxillofac Surg 2016.), the pain score in the standard of care (placebo) group immediately postoperatively was as high as 6. Assuming increased variability (standard deviation of 2.5) in the current study and a two point reduction in the opioid free group, 1:1 sampling ratio, type I error of 0.05 and power of 0.8, a total of 26 subjects per group are required. Given the expected potential for missing data, we will enroll 30 patients per group (N = 60 overall) in order to adequately power our study.

Statistical Analysis

Descriptive statistics of the data will be presented. Continuous data will be reported as mean ± standard deviations or medians (interquartile range) depending on the distribution of the data and assessed with a parametric t-test or non-parametric equivalent, as appropriate. Categorical data will be reported as frequencies and proportions and assessed with a chi-square or Fishers exact test.

Our primary outcome will be assessed by comparing the worst postoperative pain score between those who are with opioid free anesthesia (Group I) and those who are with opioid anesthesia (Group II). A t-test or non-parametric equivalent will be employed. Although we expect randomization to account for baseline differences, multivariable linear regression may be employed to assess differences in the outcomes between groups. Secondary continuous outcomes (e.g. opioid consumption) will be assessed in a similar fashion. Secondary categorical outcomes will be assessed with a chi-square test, employing logistic regression as necessary to adjust for baseline differences between groups. In the case of both linear and logistic regression, models will be adjusted for clinically relevant differences at baseline, or variables for which the p-value is < 0.10 on the univariate level. Given that some data may be collected at multiple time points (e.g. pain scores), we will employ the use of paired t-tests and repeated measures regression to account for the correlation between observations, as necessary. For all analyses two-sided p-values < 0.05 considered statistically significant.

Risks and Discomforts

This study will utilize two routinely employed intraoperative opioid strategies. Thus, there is no anticipated physical risks outside those experienced as part of their routine care.

This study will not ask any sensitive information as part of the study questionnaires; therefore this possibility of psychosocial risks is limited. As with any research study there is the possibility of a breach of confidentiality. Investigators are explicitly trained in the appropriate handling of research data. Physical (locked offices) and electronic (password protected computers) barriers will be used to ensure confidentiality.

The principal investigator, Dr. Wang, Jinping will be responsible for monitoring and assure the safety and welfare of subjects, the validity and the integrity of the data, and adherence to the IRB-approved protocol. Any events occurring prior to the study procedure will be recorded as medical history. Any adverse events (AE) that occur during the course of this trial will be recorded and will be followed until resolution, study completion or termination. Each event will be recorded as it happens (or as soon as it becomes known to study staff). Any serious or unexpected adverse events related to study, should they occur, will be expeditiously (within 5 working days) be reported to MGB IRB in accordance with the IRB reporting requirements.

Potential Benefits

It is hypothesized that use of opioid free anesthesia may lead to improved overall postoperative pain levels, less postoperative opiate medication, and shorter time to discharge from the PACU. Individual health benefits however cannot be guaranteed.

It is likely that society as a whole will benefit from increased knowledge of the role of intraoperative opioid strategies on postoperative recovery, pain and anesthesia related complications. Given the number of patients who currently undergo TMJ surgery and the rising opioid crisis, this study could have important implications for a large number of patients.

Data Collection, Source Documents and Confidentiality

Data will be collected in a study specific REDCap (Research Electronic Data Capture) account hosted on a MGB server. Data collection for this study includes but is not limited to:

- Demographic data (age, race, ethnicity, height, weight, body mass index, sex)
- Baseline medical comorbidities
- Surgical characteristics (ex. repeated surgery, unilateral/bilateral, duration)
- Intraoperative and postoperative medication administration (opioids and adjuvants)
- Pain scores and pain satisfaction survey data
- Postoperative complications (ex. ileus, nausea, vomiting)
- PACU and hospital characteristics (ex. length of stay, unplanned admission)

All participating investigators have received human subjects training. Study data will be maintained in a secure and encrypted environment (locked in the PI's office) or REDCap and the data will be kept on a password protected hospital PC accessible to only study investigators. Computers and data collected on paper will be stored in locked rooms. For all analyses subjects will be identified only by their unique coded study ID number assigned for the sole purpose of this project. Access to the study crosswalk will be restricted to the study staff included on the protocol. Limited information will be retained on patients who are prescreened and do not qualify, or who are approached and declined, for the purposes of generating a CONSORT diagram for the trial. The principal investigator will ensure the safety and integrity of all study data and the confidentiality of individual participants.

Throughout the life of the study the principal investigator and study staff will be responsible for monitoring the validity and integrity of data. The principal investigator and/or study staff will review the accuracy and completeness of reports, documents, and informed consents. The principal investigator will monitor adherence to patient confidentiality and other applicable guidelines and will be responsible for overall study performance. The Principal Investigator will therefore be responsible for data integrity, and will ensure study compliance with the IRB approved protocol and applicable regulations.