PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

INSTRUCTIONS

- This should include a referenced systematic evidenced-based review when possible.
- If this study involves qualitative research explain the major constructs of your study.
- Do not state in this section what you plan to do in this study. This information should be entered later under "What will be done in this protocol?"
- Do not include the bibliography in this section.
- For studies submitted under the Expedited review criteria, this section need not be more than a few paragraphs.
- For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/ procedures/data points.
- If this is an update to current templates from Protocol Builder make sure the information throughout the protocol includes the most current information.

Answer/Response:

Total shoulder arthroplasties are increasingly taking place in the outpatient setting. As such, having a robust post-operative pain management strategy is important. These should include multimodal analgesia and regional anesthesia. Regional anesthesia in the ambulatory center allows for adequate and fast control of post-operative pain and is able to facilitate early discharge (1). However, the phenomenon of rebound pain can be a significant driver for worsening post-operative pain, leading to increased healthcare utilization, ER visits and possible readmission for inadequate pain control. Since only patients that get regional blocks can develop rebound pain and the fact that blocks have not been definitively shown to alter pain trajectories over time when compared to patients that do not get nerve blocks (1), it is important to develop strategies to mitigate this potentially painful circumstance.

Rebound pain has been increasingly studied in recent years. It has been shown that orthopedic surgery in itself is associated with rebound pain after nerve blocks, with upper limb surgery more commonly correlated with the phenomenon than lower limb surgery (2). Many definitions of rebound pain have been proposed, including " the transition from well-controlled pain (numerical rating scale [NRS] <3) while the block is working to severe pain (NRS >7) within 24 h of block performance." (3) These definitions lead to an incidence rate of up to 50% in some studies (3). Factors associated with rebound pain include younger age, female gender, bone surgery, and absence of IV dexamethasone dosing (3). Some strategies, like providing a dose of strong short acting opioid at the predicted time of block resolution, did not show promise in preventing rebound pain (4).

To date, there have not been any studies relating local anesthetic concentration to rates of rebound pain. Though lower concentrations of local anesthetic could theoretically reduce the time of nerve blockade, local anesthetic dose in milligrams has been more correlated with block length than concentration alone (7). There are studies that show even a low dose of bupivacaine can be effective at reducing post op pain scores and facilitating early discharge from an ambulatory center (8). At the University of Virginia, two different concentrations of bupivacaine (0.5% and 0.25%) are used interchangeably per anesthesiology preference. That means that the choice between 0.5% and 0.25% bupivacaine is made by the attending anesthesiologist based on clinical judgment. Selection may consider physician experience and patient-specific factors such as age, weight, health status, and procedure type, but there is no formal guideline mandating one concentration over the other. Both concentrations are routinely considered safe and effective.
We have designed a pilot study to better understand the relationship between local anesthetic concentration and rebound pain.

Objectives/Hypothesis

INSTRUCTIONS:
If this study involves biomedical research clearly state the objectives and hypotheses and clearly define the primary and any secondary outcome measures. If this study involves qualitative research clearly state your research hypothesis or question.

This section should not include information already included in other sections such as background information or information from the procedures section.

Answer/Response:

Purpose:
This pilot study aims to assess the feasibility of collecting post-operative pain data and to explore potential differences in pain trajectories based on the concentration of local anesthetic used.

Primary Objective:
To explore the relationship between bupivacaine concentration (0.25% vs. 0.5%) and the severity of rebound pain following shoulder arthroplasty.

Hypothesis:
Patients receiving a lower concentration of local anesthetic (0.25% bupivacaine) will experience lower severity of rebound pain compared to those receiving a higher concentration (0.5%).

Primary outcome:
Maximum NRS pain score within 24 hours from the completion of the nerve blocks and time of perceived block resolution

Secondary outcomes:
1. NRS: pain scores from the completion of the nerve blocks and every 4 hours while awake, for 72 hours.

2. Total opioid consumption converted to Morphine Milligram Equivalents (MMEs) during the first 72 hours post-op.
3. Self-reported sensory block duration (time to nerve blocks resolution).

Study Design: Biomedical

1. Will controls be used?
Answer/Response:No

►IF YES, explain the kind of controls to be used.
Answer/Response:

2. What is the study design?

Example: case series, case control study, cohort study, randomized control study, single-blind, double-blind, met-analysis, systematic reviews, other. You may also view the IRB-HSR Learning Shot on this topic to help you answer this question.
Writing a Clinical Research Protocol

Answer/Response: Single Blind Randomized Study-the subject will be blinded to which concentration of medication is assigned.

3. Does the study involve a placebo?
Answer/Response: No

►IF YES, provide a justification for the use of a placebo
Answer/Response:

Human Participants

Ages: greater than or equal to 18 years old
Sex: Any
Race: Any

Subjects- see below

INSTRUCTIONS: For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.

1. Provide target # of subjects (at all sites) needed to complete protocol.

INSTRUCTIONS: If this is NOT a database protocol, this number should be the same as the number of subjects needed to obtain statistically significant results.

Answer/Response: 20

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

Answer/Response: 20%

3. How many subjects will be enrolled at all sites?

INSTRUCTIONS: This number must be the same or higher than the # from question # 1 in order to account for the # of screen failures, dropouts, withdrawals described in question # 2.

Answer/Response: 26

4. How many subjects will sign a consent form under this UVA protocol?

INSTRUCTIONS: If the protocol does not have a consent form- the number listed here should reflect such things as the number of subjects from whom specimens will be obtained, the number of charts to be reviewed etc.

Answer/Response: 26

Inclusion/Exclusion Criteria

INSTRUCTIONS:

- The inclusion and exclusion criteria should be written in bullet format.
- *This item applicable if the study will require consent (verbal or written).* Unless there is a scientific reason for not recruiting a certain type of vulnerable population(e.g. not enrolling fetuses, neonates or children in a study regarding Alzheimer's) list the following vulnerable populations under either Inclusion or Exclusion criteria below: pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non- English speaking subjects .
- If you will not enroll subjects who do not speak English because certain procedures cannot be carried out if the subject does not speak English (e.g. a survey is not validated in other languages) insert the following as an Inclusion Criteria: Willingness and ability to comply with scheduled visits and study procedures.
- If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
- The stop date must be prior to the version date of this protocol.
- *Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion

Answer/Response:

1. Primary Total shoulder replacement patients (anatomic and reverse)
2. Adult patients (greater than or equal to 18 years)
3. Any gender
4. Any race

2. List the criteria for exclusion

Answer/Response:

1. Chronic Pain diagnoses including:
    a. substance/opioid use disorder
    b. complex regional pain syndromes
    c. fibromyalgia
2. Daily persistent opioid use spanning 3 months prior to surgery date
3. Allergy to local anesthetics or NSAIDS
4. Respiratory pathologies including:
    a. CPAP- non-compliant / untreated obstructive sleep apnea
    b. COPD
    c. Restrictive lung disease (pulmonary fibrosis, interstitial pneumonia, etc)
    d. Contralateral diaphragm dysfunction
5. BMI > 40
6. Ipsilateral extremity pre-existing nerve injury
7. GFR < 60
8. NSAID contraindications
9. Inability to follow up
10. Revision of shoulder replacement surgery
11. Patients requesting block as primary anesthestic (avoidance of general anesthesia)
12. Need or request for brachial plexus catheter or liposomal bupivacaine
13. Vulnerable populations (including cognitively impaired Children and Adolescents, Critically Ill or Emergency Patients or incarcerated persons)
14. non-English speaking
15. Pregnant or Lactating
16. Blind or illiterate: Participants who are blind or illiterate are excluded because the study requires independent completion of written pain records and questionnaires and transmission of photographed forms via text message. Inability to complete these procedures without assistance would compromise data validity, standardization, and confidentiality. The exclusion is methodological and related to study feasibility rather than to the condition itself.

3. List any restrictions on use of other drugs or treatments.

INSTRUCTIONS: List only those drugs or treatments that are prohibited while on study, not those listed as an exclusion criteria.

Answer/Response: There are no other restrictions on the use of other medications or treatments apart from those related to substance/opioid use disorder.

None Statistical Considerations

1. Is stratification/randomization involved?

Answer/Response: yes

►IF YES, describe the stratification/ randomization scheme.

INSTRUCTIONS:
The stratification factors and/or the randomization plan should be identified. If there is no randomization component or important patient characteristics that will be used in treatment allocation or data analysis, a statement to this effect should be included.

Stratification factors: These are pretreatment patient characteristics which could be balanced across treatment arms by design or may be used to determine starting dose or treatment allocation.

If randomization is going to be used, the details of the randomization plan should be described.

The description should include:
--the method and timing of randomization
--the type of randomization scheme that will be used in the study
--whether or not the randomization masked/blinded/if so, then to whom is it masked/blinded
--who has access to the randomization scheme

Answer/Response:
Randomization will be done with a random number generator to be delivered on a sealed envelope to the provider preparing the drug to be opened after the patient signs the consent.

►IF YES, who will generate the randomization scheme?

_____ Sponsor
_____ UVA Statistician. Insert name Answer/Response:
_____ UVA Investigational Drug Service (IDS)
_X____ Other: Specify Answer/Response: Siny Tsang, PhD a Biostatistician from Dept of Anesthesiology

2. What are the statistical considerations for the protocol?

The objectives section and the statistical section should correspond, and any objective for which analysis is unfeasible should be deleted. Also, the estimates and non-statistical

assumptions of the statistical section should be supported by discussion in the background section.

The answer to this question should include:
--Study Design/Endpoints
--Recap of study objectives and endpoint definitions. An assessment of how study objectives will be assessed by identifying & defining which endpoints will be used to assess each component of the study objectives.
--The study design should include contingencies for early stopping, interim analyses, stratification factors (If applicable), and any characteristics to be incorporated in analyses.
--The power/precision of the study to address the major study endpoint(s), the assumptions involved in the determination of power/precision.
--If statistical hypothesis testing is included then specify the null and alternative hypotheses, the test statistic, and the type I and II error rates
--If precision of an estimate, then provide a definition for precision
--If other, then specify

Answer/Response:
--The Study is a Single Blinded Randomized Study, with the endpoint being "Maximum NRS pain score within 24 hours from the completion of the nerve blocks"
-- Objective: To explore the relationship between bupivacaine concentration (0.25% vs. 0.5%) and the severity of rebound pain following shoulder arthroplasty.
--- Endpoint definitions:
Primary:
Maximum NRS pain score within 24 hours from the completion of the nerve block and time to perceived block resolution
Secondary:
1. NRS: pain scores from the completion of the nerve blocks and every 4 hours while awake, Collected via pain diary for 72 hours.
2. Total opioid consumption (converted to MMEs) during the first 72 hours post-op and collected via pain diary.
3. Self-reported sensory block duration (time to nerve blocks resolution).

-- There are no conceivable reasons for stopping the study early, as these two concentrations, dosages, techniques are used daily already. There are no additional safety reasons to do so. We do not plan to do interim analysis. We will not stratify.

Although a hypothesis is stated, this study is designed as an exploratory pilot trial and is not powered to formally test statistical hypotheses.
Null and alternative hypotheses are therefore not formally specified, and no definitive hypothesis testing is planned. The primary endpoint (maximum NRS pain score within 24 hours)

will be analyzed descriptively and using exploratory comparative statistics to estimate effect sizes and variability between the 0.25% and 0.5% bupivacaine groups.
As a result, Type I and Type II error rates are not controlled, and the study is not intended to draw confirmatory conclusions. Findings will be used to inform sample size calculations and statistical planning for a future adequately powered randomized controlled trial.

3. Provide a justification for the sample size used in this protocol.

Include sample size calculations or statistical power estimation. If not applicable, please provide explanation. Also include the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate, adjustments for drop-outs etc. and study duration.

Answer/Response:
The proposed sample size intends to evaluate the feasibility of the data collection process, regarding the pain diaries once the patients are discharged. The sample size of n = 10 per bupivacaine concentration group, plus n=6 to compensate the expected 20% dropouts (total N = 26) intends to provide the investigating team pilot data in order to estimate the sample size for a full study. No a priori power analysis is required for this study this is intended to be a pilot study.

4. What is your plan for primary variable analysis?

Include primary outcome(s)/predictor variable(s), statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation.

Answer/Response: Descriptive statistics of the primary outcome variable (maximum NRS pain score within 24 hours) will be computed, separately by group. Linear regression models will be used to explore potential differences between the two groups, but results are not to be interpreted as inferential due to the nature of the proposed pilot study.

5. What is your plan for secondary variable analysis?

Include the following: --Secondary outcome(s)/predictor variables, statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation. --For phase III studies, the power/precision of the study to address the secondary objective(s).

Answer/Response: Similar descriptive statistics will be performed for the secondary variables, as described above. For those randomized to the pain diary condition (see below), compliance rates (frequencies and proportions) will be evaluated across the three postoperative days. We will also assess the extent to which the maximum pain scores differ between patients who were randomized into the pain diary condition versus those randomized into the phone call condition.

6. Have you been working with a statistician in designing this protocol?

Consultation with a professional statistician is highly recommended to ensure good science of the study and facilitate the review process.

Answer/Response: Yes

IF YES, what is their name?

Answer/Response: Siny Tsang, PhD

7. Will data from multiple sites be combined during analysis?

Answer/Response: No

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?

Answer/Response:

IF YES, will randomization be done at each site or among sites?

Answer/Response:

7(b). Has the sample size calculation considered the variation among sites?

Answer/Response:

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

Answer/Response:

7(d). Is there a common protocol used in all sites?

Answer/Response:

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?

Answer/Response:

Study Procedures-Biomedical Research

1. **What will be done in this protocol?**

INSTRUCTIONS:
This should include everything that will be done as part of this protocol. Do not repeat information that is included in other sections such as Background or Hypothesis sections.
This section should include an indication of which research interventions if any offer a prospect for direct benefit and which interventions (invasive measurements, collection of blood, tissue, data, surveys, etc.) are being done solely to answer a research question and generate generalizable knowledge. If the interventions done solely for research purposes are associated with greater than minimal risk they need to be justified. Describe and justify any control and experimental arm and include method, dose, and duration of drug administration. Reference any claim of clinical equipoise if applicable.

If you are obtaining specimens or data, provide information regarding the type of specimen/data, amount of specimen needed and how the specimen/data will be obtained and what analysis will be done with the specimen/data.

Special note for studies with waiver of consent/waiver of documentation of consent:
Include a statement regarding how subjects will be recruited. For other studies this information is captured in Recruitment does not need to be duplicated in this section.

Answer/Response:

Study Procedure

Following the informed consent process, enrolled participants will undergo study procedures as described below. Participants will not know which anesthetic concentration they get, but they will know which way their data is being collected. They will be randomized in a **2×2 factorial design** with two independent factors:

1. **Local anesthetic concentration for the nerve block**, and
2. **Pain data collection method.**

Randomization Factor 1: Local Anesthetic Concentration

Participants will be randomized to receive one of the following nerve block solutions:

- **Drug Concentration 1:** 0.5% plain bupivacaine
- **Drug Concentration 2:** 0.25% plain bupivacaine

All regional blocks will be performed in the pre-operative area by a trained regional anesthesiologist or a regional anesthesiology fellow using a standardized technique.

Randomization Factor 2: Pain Data Collection Method

Participants will also be randomized to one of two methods for postoperative pain assessment:

- **Data Collection Method 1 (Paper Diary):**
  Participants will receive a paper diary and will be instructed to document pain scores every 4 hours (±1 hour) while awake for 24, 48, and 72 hours following completion of the nerve block , and to take a picture of it at the end of each day for 3 days.
    - **Pain Score #1:** On a scale of 0–10, with 10 representing the worst pain imaginable, what is your current pain score?
    - **Pain Score #2:** On a scale of 0–10, with 10 representing the worst pain imaginable, what was your highest pain score during the previous 4 hours? Participants will also document the date and time they perceive the block to be no longer effective (e.g., when sensation or movement returns in the affected extremity).

    Participants will be asked to send a photo of the diary via text message to the research team each day

- **Data Collection Method 2 (Telephone Follow-Up):**
  Participants will be contacted by a member of the study team via telephone at approximately 24, 48, and 72 hours following completion of the nerve block. During each call, the following information will be obtained:
    - **Question #1:** On a scale of 0–10, with 10 representing the worst pain imaginable, what was your highest pain score during the past 24 hours?
    - **Question #2:** What is the date and time you believe the block was no longer effective (e.g., when sensation or movement returned in the affected extremity)?

Pain Medication Diary

All participants, regardless of randomization assignment, will be instructed to maintain a **pain medication diary** for 72 hours following completion of the nerve block. Participants will record the date, time, and dose of all medications taken for pain management, including opioids, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), cannabis products, or other analgesics. Cannabis use in this study is assumed to be legally obtained through medical use by individuals aged 21 or older in the state of Virginia. The study does not encourage, provide, or facilitate cannabis use. Cannabis use is recorded only as self-reported exposure for observational purposes. If a participant discloses cannabis use that may be illegal (e.g., recreational use by someone under 21), the information will be handled as confidential research data, consistent with IRB-approved confidentiality protections. Such disclosures will not be reported to authorities, unless required to address an immediate safety concern and for

other research-related reasons as outlined in the "Who will see your private information?" of the consent form.

For participants in the Data Collection Method 1 (Paper Diary) group, the pain medication diary will be incorporated into their paper diary tracking pain scores. For the Data Collection Method 2 (Telephone Follow-Up) group, participants will be asked to take a photo of the medication log and send it via text message to the study team each day.

Review of Medical Records

The study team will also review the surgical notes and medical history from the participants' medical records for research purposes.

2. **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**

Example: If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
Instructions: Answer NA if this study does not involve a study treatment.

Answer/Response: NA, this is a one time only dose in which both concentrations are used interchangeably at UVA as part of routine care for subjects undergoing shoulder replacement surgery.

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
(e.g. study team will administer study drug/ study interventions, study drug inventory of dispensed and returned drug, diary etc.)
Answer/Response:.
All subjects will receive instructions on how to complete the pain medication diary and about being available to answer phone calls from study coordinators at 3 timepoints over 3 days. Subjects will receive instructions about how to complete the pain diary, and they also be asked to photograph their pain diary daily and send the photograph via text message to the Clinical Research Coordinator to a department issued cell phone. All subjects will be asked to photograph the medication diary daily and send the photograph via text message to the Clinical Research Coordinator on a department issued cell phone. This procedure will make sure the diary is complete everyday and in case it is lost or not returned the data will still be available. The study patient population is an older one and we are trying to simplify data collection for them using a paper

format. The subject diary will only have the subject's research number on it, therefore the data security risk is minimized.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
(e.g. subject returns more than 20% of the study drug, subject misses 20% of study visits)
Answer/Response:
Non-compliance for our study would be failure to return phone calls or failure to return the pain diary.

Bibliography

INSTRUCTIONS: Provide a current bibliography supporting the hypothesis, background and methodology including references to papers and abstracts that have resulted from previous work by the investigator and references to the work of others.

1. Lavand'homme P. Rebound pain after regional anesthesia in the ambulatory patient. Current Opinion in Anaesthesiology. 2018 Dec;31(6):679–84.
2. Abdallah FW, Halpern SH, Aoyama K, Brull R. Will the Real Benefits of Single-Shot Interscalene Block Please Stand Up? A Systematic Review and Meta-Analysis. Anesthesia & Analgesia. 2015 May;120(5):1114–29.
3. Barry GS, Bailey JG, Sardinha J, Brousseau P, Uppal V. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. British Journal of Anaesthesia. 2021 Apr;126(4):862–71.
4. Uppal V, Barry G, Ke JXC, Kwofie MK, Trenholm A, Khan M, et al. Reducing rebound pain severity after arthroscopic shoulder surgery under general anesthesia and interscalene block: a two-centre randomized controlled trial of pre-emptive opioid treatment compared with placebo. Can J Anesth/J Can Anesth. 2024 Jun;71(6):773–83.
5. Woo JH, Lee HJ, Oh HW, Lee JW, Baik HJ, Kim YJ. Perineural dexamethasone reduces rebound pain after ropivacaine single injection interscalene block for arthroscopic shoulder surgery: a randomized controlled trial. Reg Anesth Pain Med. 2021 Nov;46(11):965–70.
6. Lee HJ, Woo JH, Chae JS, Kim YJ, Shin SJ. Intravenous Versus Perineural Dexamethasone for Reducing Rebound Pain After Interscalene Brachial Plexus Block: A Randomized Controlled Trial. J Korean Med Sci. 2023;38(24):e183.
7. Fredrickson MJ, Abeysekera A, White R. Randomized Study of the Effect of Local Anesthetic Volume and Concentration on the Duration of Peripheral Nerve Blockade: Regional Anesthesia and Pain Medicine. 2012;37(5):495–501.
8. Al-Kaisy A, McGuire G, Chan VW, Bruin G, Peng P, Miniaci A, et al. Analgesic effect of interscalene block using low-dose bupivacaine for outpatient arthroscopic shoulder surgery. Reg Anesth Pain Med. 1998;23(5):469–73.