CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL PRODUCT(S):	Not Applicable
STUDY NUMBER(S): **IRB Number**	
Other Protocol Identifiers	
PROTOCOL(S) TITLE:	Ultrasound-Guided Genicular Nerve Block for Knee Pain in the Emergency Department: A Randomized Controlled Trial
NUMBER:	
REGULATORY SPONSOR:	
FUNDING SPONSOR(S):	Not applicable.
MEDICAL DIRECTOR	Michael Shalaby, MD
ORIGINAL PROTOCOL DATE:	
VERSION NUMBER:	**Version 2.0**
VERSION DATE:	**5/16/2025**

PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	Not applicable.
STUDY TITLE:	Ultrasound-Guided Genicular Nerve Block for Knee Pain in the Emergency Department: A Randomized Controlled Trial
STUDY ID	
PROTOCOL VERSION	

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name	Michael Shalaby	Signature	
Affiliation:	Department of Emergency Medicine	Date	**3/19/2025**

Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center

OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SoA	Schedule of Activities
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem
US	United States
GNB	Genicular Nerve Block
SMGN	Superomedial Genicular Nerve
SLGN	Superolateral Genicular Nerve
IMGN	Inferomedial Genicular Nerve
ILGN	Inferolateral Genicular Nerve
OA	Osteoarthritis
EM	Emergency Medicine
ED	Emergency Department
LAST	Local Anesthetic Systemic Toxicity
APS-POQ-RED	American Pain Society-Patient Outcome Questionnaire-Revised for the ED
NSAID	Non-Steroidal Anti-inflammatory Drug
NRS	Numeric Rating Scale
Cedar	HUP Cedar
RCT	Randomized Clinical Trial
PAH	Pennsylvania Hospital
HUP	Hospital of the University of Pennsylvania
PPMC	Penn Presbyterian Medical Center

1 STUDY SUMMARY

1.1 Synopsis

Title:	Ultrasound-Guided Genicular Nerve Block for Knee Pain in the Emergency Department: A Randomized Controlled Trial
Short Title:	Genicular Block for Knee Pain: An RCT
Study Description:	Patients who present to the emergency department (ED) at any of the clinical sites of the University of Pennsylvania Heath System with atraumatic knee pain will be considered for enrollment to be randomized to receive an ultrasound-guided genicular nerve block (GNB) or conventional analgesia. Patients randomized to the intervention arm will receive a three-point GNB with weight-based dosing 0.5% bupivacaine augmented with 4 mg dexamethasone, divided into three separate aliquots to be injected around the superomedial genicular nerve (SMGN), superolateral genicular nerve (SLGN), and inferomedial genicular nerve (IMGN). This will be an open-labeled, investigator-initiated study with convenience enrollment.
Objectives:	Primary Objective: • To determine whether patients receiving a GNB for knee pain experience greater pain reduction compared to conventional analgesia Secondary Objectives: • To determine whether patients who receive a GNB experience a longer duration of analgesia compared to those who receive conventional analgesia • To determine whether patients who receive a GNB report higher patient satisfaction compared to those who receive conventional analgesia • To determine whether patients who receive a GNB have shorter ED length of stay (LOS) compared to those who receive conventional analgesia
Primary Endpoint:	• Difference in pain level as measured by NRS at pre-intervention (GNB or conventional analgesia) and at either 1-hour post-enrollment or time of ED discharge, whichever occurs first

Secondary Endpoints:	• Difference in duration of analgesia, assessed at 24-36 hours post intervention. • Difference in APS-POQ-RED between treatment arms, assessed at either 1-hour post-enrollment or time of ED discharge, whichever occurs first. • Difference in ED LOS between treatment arms, as determined by time from enrollment in study to time of ED discharge.
Study Population:	Patients presenting with knee pain at any of the four emergency departments: (1) Hospital of the University of Pennsylvania (HUP), (2) Penn Presbyterian Medical Center (PPMC), (3) Pennsylvania Hospital (PAH), and (4) HUP Cedar (Cedar) All genders, age ≥ 18, all demographic groups Moderate to severe knee pain (pain measured on NRS between 5 and 10) Exclusions based on general health status: cognitive impairment / dementia, inability to consent for study procedure Exclusion criteria: pregnant; incarcerated; large knee joint effusion as identified on plain film radiography; acute traumatic etiology for knee pain including fracture, dislocation, or suspected tendonous or ligamentous injury; concern for infection including septic joint, abscess, cellulitis, or sepsis; hemodynamic instability; allergy or contraindication to bupivacaine or any of its components Sample size: 17 patients per treatment arm
Phase:	N/A
Description of Sites/Facilities	(1) Hospital of the University of Pennsylvania (2) Penn Presbyterian Medical Center (3) Pennsylvania Hospital (4) HUP Cedar
Enrolling Sites:	EDs of the four previously mentioned sites
Description of Study Intervention:	The study intervention is an ultrasound-guided three-point GNB, which involves injection of local anesthetic with adjuvant (ideal bodyweight-dosed bupivacaine 0.5% and dexamethasone 4 mg) around the genicular nerves of the knee. The genicular nerves are a series of four terminal

	sensory nerve branches of the femoral nerve that provide sensory innervation to the joint capsule of the knee, thereby providing pain relief without motor blockade or paralysis. See detailed description of the study intervention in Section 6. The comparison control arm involves conventional analgesia for knee pain, which includes oral, intravenous, or topical analgesics (e.g., acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], opioids, lidocaine patches, heating or cold packs) and will be determined at the discretion of the primary provider caring for the patient. See detailed description of study control arm in Section 6.
Study Duration:	12-months
Participant Duration:	24 to 36-hours Participant duration will end at 24 to 36-hours after treatment, at which time a research assistant or the participating physician will contact the patient via telephone call to assess for duration of analgesia. (See Section 4.4 for complications which would extend participation duration beyond 24 to 36 hours.)
Resources Necessary for Human Research Protection	This study is being conducted by the Division of Ultrasound within the Department of Emergency Medicine. The Principal Investigator is an ultrasound faculty member. The other investigator is an emergency medicine resident. Other research staff include a biostatistician, the ultrasound division's clinical research coordinator, and the research assistants within the Emergency Medicine Academic Associates program. All staff participating in the research will be trained on the protocol. Prior to the initiation of enrollment, the PI and co-investigator will meet with the research assistants to discuss recruitment including establishing an EPIC Haiku notification system, as well as inclusion and exclusion criteria. The clinical research coordinator is trained on data storage in REDCap. All resources required to complete this randomized controlled trial are provided by the Department of Emergency Medicine and the Division of Ultrasound, including the research assistants, the clinical research coordinator, and the biostatistician. Progress of the trial will be discussed at least every other week at the research meetings within the Division of Ultrasound.

1.2 Key Roles and Study Governance

Sponsor	*Medical Director*
Not Applicable	Michael Shalaby, MD
	Department of Emergency Medicine, Hospital of the University of Pennsylvania
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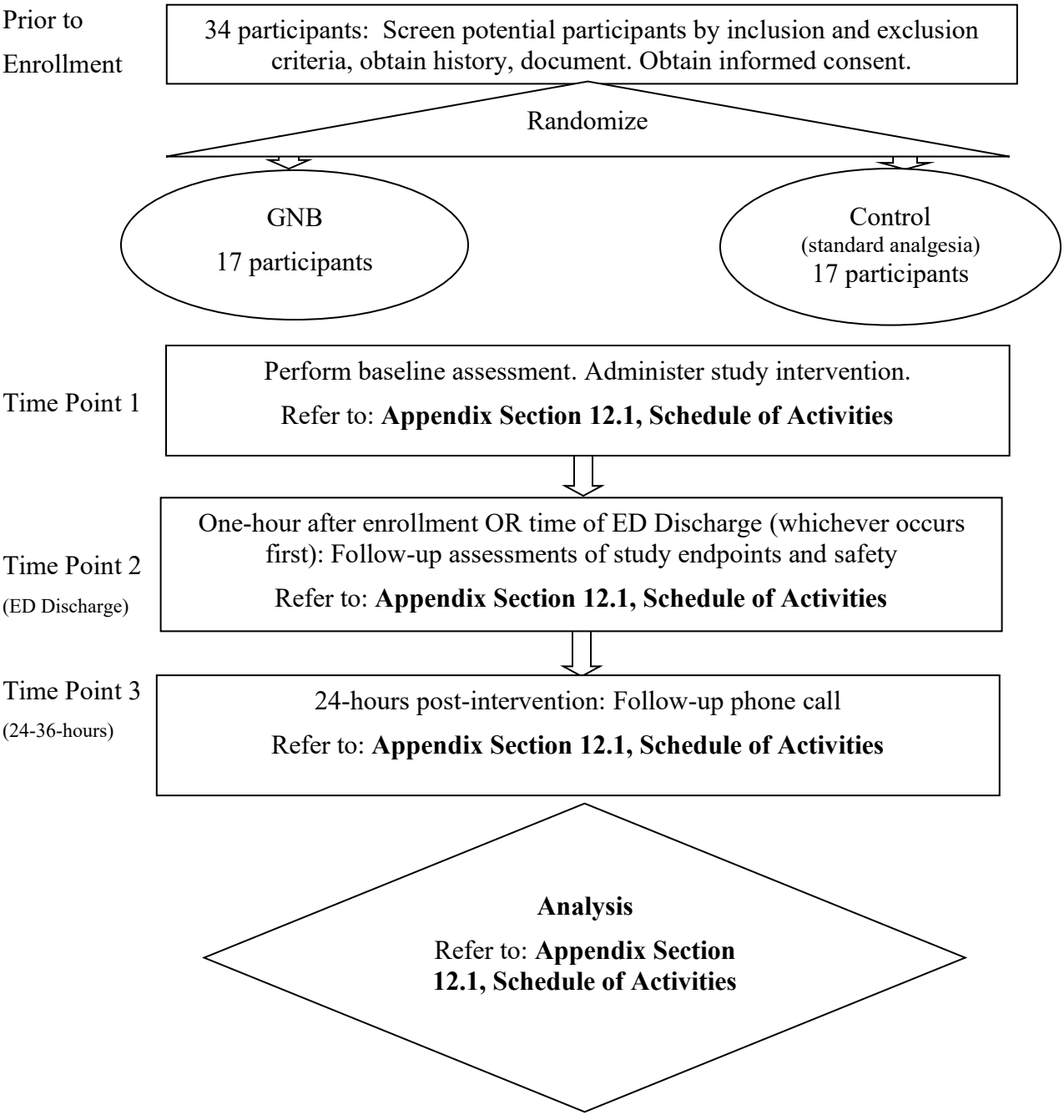
1.3 Schema


Prior to Enrollment
34 participants: Screen potential participants by inclusion and exclusion criteria, obtain history, document. Obtain informed consent.
Randomize
GNB
17 participants
Control
(standard analgesia)
17 participants
Time Point 1
Perform baseline assessment. Administer study intervention.
Refer to: Appendix Section 12.1, Schedule of Activities
Time Point 2
(ED Discharge)
One-hour after enrollment OR time of ED Discharge (whichever occurs first): Follow-up assessments of study endpoints and safety
Refer to: Appendix Section 12.1, Schedule of Activities
Time Point 3
(24-36-hours)
24-hours post-intervention: Follow-up phone call
Refer to: Appendix Section 12.1, Schedule of Activities
Analysis
Refer to: Appendix Section 12.1, Schedule of Activities

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Knee osteoarthritis (OA) is extremely prevalent, with a global incidence of greater than 20% of adults with age greater than 40 years (Cui 2020). Flares of chronic knee OA pain are common and are a frequent reason for presentation to the emergency department (ED). ED evaluation and management of exacerbations of chronic knee pain in patients with OA typically involves plain film radiography to evaluate for acute fracture or worsening of disease followed by oral, topical, or intravenous analgesics. However, these conventional therapies may often provide limited benefit in the acute setting and can be contraindicated in patients with certain concomitant comorbidities. In particular, the use of non-steroidal anti-inflammatory drugs is often limited in patients on anticoagulation or those with gastritis, gastrointestinal ulcers, gastrointestinal bleeding, or chronic kidney disease. Opioids are also commonly used in the acute setting for multiple causes of musculoskeletal pain, including exacerbations of chronic knee pain. One study reported that nearly 17% of patients discharged from the ED received a prescription for opioids (Hoppe 2015). While opioids are highly effective for acute pain management, they are associated with numerous adverse effects including respiratory depression, central nervous system effects, nausea, vomiting, and constipation, especially in elderly patients or those with certain comorbidities. Moreover, prolonged opioid use increases the risk for developing tolerance and dependence, which often leads to withdrawal, overdose, and death (Paul 2021). For this reason, identifying safe and effective alternatives to opioid analgesia is a research area of high priority in emergency medicine (Rech 2022).

According to a 2017 practice guideline published by the American Academy of Emergency Medicine, “effective, efficient, and safe pain management is a cornerstone of state-of-the-art patient care in the ED and is a specialty-defining skill” and “emergency clinicians should consider regional and local nerve blocks for traumatic and nontraumatic painful conditions, alone or in combination with pharmacological and nonpharmacological treatment modalities.” With increased training and proficiency in ultrasound, emergency physicians are more commonly utilizing ultrasound-guided regional anesthesia techniques to facilitate multimodal pain control in the ED. The American College of Emergency Physicians released a policy statement in 2021 endorsing that ultrasound-guided nerve blocks are “not only within the scope of the practice of emergency physicians, but represent a core component of a multimodal pathway to control pain for patients in the emergency department.” Development and implementation of safe alternative modes of analgesia may help to effectively manage breakthrough pain associated with knee OA and other etiologies of atraumatic knee pain without high doses of opioids or other potentially harmful non-opioid analgesics.

2.2 Background

The genicular nerve block (GNB) is a relatively new regional anesthesia technique that has been used for a variety of operative and non-operative indications (Yasar 2015). There are four

distinct genicular nerve branches that the knee joint: the superolateral genicular nerve (SLGN), superomedial genicular nerve (SMGN), inferomedial genicular nerve (IMGN), and inferolateral genicular nerve (ILGN). The GNB classically involves deposition of a small volume of local anesthetic around the SLGN, SMGN, and IMGN. Due to the proximity of the ILGN to the tibial nerve, blockade of the ILGN is often avoided to minimize the risk of foot drop from inadvertent blockade of the tibial nerve (Sobel 2021). While this technique can be performed solely by landmark guidance, evidence favors utilizing ultrasound guidance, as the genicular nerves and associated genicular vascular structures can be easily visualized with real time ultrasound guidance (Singh 2023).

The safety and efficacy of the GNB using perineural bupivacaine has been extensively evaluated, and studies within the orthopedic and rheumatology literature have demonstrated effective pain control of knee OA for up to three months following a single set of genicular nerve blocks (Tan 2022). While several isolated cases of the GNB have been reported in the EM literature for knee OA and tibial plateau fractures (Bhattaram 2024, Kong 2023, Sobel 2021), no larger comparative studies or interventional trials have evaluated the utility of the GNB among ED patients who present with breakthrough knee pain.

2.2.1 Pharmacokinetics, Pharmacodynamics and Toxicology

Mechanism of Action: Bupivacaine binds to the intracellular portion of voltage-gated sodium channels, thereby blocking sodium influx into neurons, preventing depolarization and subsequently preventing conduction of pain signals

Onset of Action: 1 to 17 minutes (dose dependent)

Duration of Action: 2 to 9 hours, depending on dosing; up to 24-hours with adjuvants

Half-Life: 2.7 hours (in adults)

Time to Peak Plasma Concentration: 30 to 45 minutes (for peripheral infiltration)

Protein Binding: approximately 95%

Metabolism: Primary hepatic metabolism in conjunction with glucuronic acid. Pipecoloxylidine is the major metabolite of bupivacaine.

Excretion: Renal (4-10%)

(Shafiei 2023, Becker 2012)

2.2.2 Assessment for Potential Study Products Drug-Drug, Drug-Device, Device-Device Interactions

Potential interactions of bupivacaine include:

Local Anesthetics: Toxic effects of local anesthetics are additive, such that administration of multiple anesthetics can increase the risk of systemic toxicity if greater than weight-based dosing limit.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Co-administration of bupivacaine with these agents can produce severe, prolonged hypertension if administered systemically.

Ergot-Type Oxytocic Drugs: Co-administration of bupivacaine with these agents can produce severe, prolonged hypertension or cerebrovascular accidents if administered systemically.

Nonselective Beta-Adrenergic Antagonists: Co-administration of bupivacaine with these agents can cause severe hypotension and bradycardia if administered systemically.

Drugs Associated with Methemoglobinemia: Co-administration of bupivacaine with the following classes of agents can increase risk of developing methemoglobinemia: Nitrates (nitric oxide, nitroglycerin, nitroprusside, nitrous oxide), Antineoplastic agents (cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase), Antibiotics (dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides), Antimalarials (chloroquine, primaquine), Anticonvulsants (phenobarbital, phenytoin, sodium valproate).

2.2.3 Clinical Adverse Event Profile

General Adverse Effects: nausea, vomiting, chills or shivering, headache, back pain, sexual dysfunction, restlessness, anxiety, vertigo

Local Anesthetic Systemic Toxicity (LAST): CNS Reactions (perioral tingling, tongue paresthesia, dizziness, tinnitus, blurry vision, tremors, seizures, myoclonic jerks), Cardiovascular Reactions (cardiovascular collapse, bradycardia, hypotension, cardiac arrest, ventricular arrhythmia)

Allergic Reactions: urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and severe hypotension

2.2.4 Dosing Rationale

The weight-based maximal safe dosing for bupivacaine is 2.5 mg/kg. To minimize the risk of LAST, we will utilize weight-based dosing at 80% of the maximal safe dosing which will allow for effective and prolonged analgesia while minimizing the risk of complications and LAST. Patients with body mass index (BMI) greater than 25 kg/m^2 will receive a total of 80% of their ideal body weight dosing in bupivacaine. Patients with a BMI of equal to or less than 25 kg/m^2 will receive a total of 80% of their actual body weight dosing in bupivacaine. This total dose will

be divided into three equal aliquots that will be injected around each of the three targeted genicular nerves. The use of dilute bupivacaine (0.5%) will allow for better spread to target nerves as well as a slower injection rate of anesthetic which is safer for monitoring for symptoms of LAST.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Manufacturer Drug Information:

LAST: As with all local anesthetics, the principal risk of bupivacaine is LAST, as previously described. To mitigate the risk of this, (1) anesthetic will be dosed by ideal body weight to not exceed the limit of safe dosing (e.g., 80% of maximal safe dosing by ideal body weight in patients with BMI greater than or equal to 25 kg/m^2 and actual body weight in patients with BMI less than 25 $kg/m^{2)}$, (2) anesthetic will be administered slowly to identify any early signs of toxicity, (3) aspiration will be performed prior to each injection to ensure anesthetic will not be administered intravascularly, and (4) real-time ultrasound guidance with color doppler will be performed to visualize blood vessels to ensure anesthetic is not being administered intravascularly. The risk of LAST is extremely low (<1/10,000) (Neal 2018).

Bleeding: With any percutaneous procedure, there is a risk of superficial and deep tissue bleeding. To minimize this risk, continuous real-time ultrasound visualization of the injection needle will be performed to ensure vasculature is not compromised.

Infection: With any percutaneous procedure, there is a risk of soft tissue infection. To minimize this risk, the skin overlaying the injection sites will be prepped in standard fashion with chlorhexidine, sterile ultrasound probe covers will be used, operators will wear sterile gloves, and single-single use sterile needles will be used for each injection.

Alternative Procedures: Considered using higher concentrations (0.75%), and while these have been proven safe for peripheral use, we elected to proceed with lower concentration (0.5%) for safety. Preliminary (non-published) data suggests that weight-based dosing of 0.5% bupivacaine can produce desired anesthesia. We will use ultrasound-guidance rather than landmark-guidance to visualize and avoid the genicular arteries that lay in proximity to the genicular nerves (Callese 2023).

2.3.2 Known Potential Benefits

Patients with knee OA can often have flares of severe pain, requiring ED visits for pain control. Several case reports and small case series have demonstrated the efficacy and safety of the genicular block performed in the emergency department for managing acute on chronic pain associated with knee osteoarthritis (Bhattaram 2024, Kong 2023, Sobel 2021). Moreover, a recent randomized controlled trial published in the rheumatology literature on ambulatory

patients demonstrated the that the genicular nerve block provides longer term pain relief in patients with knee osteoarthritis (Shanahan 2022). In this study, patients treated with a one-time three-point ultrasound-guided GNB reported improvements in pain scores and decreased disability as measured on the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) and the Intermittent and Constant Osteoarthritis Pain scale compared to the control group who received a sham injection for up to 12-weeks after the block (Shanahan 2022). Immediate potential benefits include improved or relief of knee pain, improved mobility and ability to ambulate, reduced need for alternative analgesics (including opioids), reduced need for admission for pain control and need for inpatient physical therapy evaluation and treatment, quicker disposition from the emergency department due to quick and effective pain control. Moreover, in our anecdotal experience, patients whom we have treated with a GNB have reported high levels of satisfaction with the procedure and have reported complete pain relief for greater than 24-hours after the block. Even when symptoms began to return, patients reported that they were not as severe as those which initially promoted them to visit the ED. Moreover, to our knowledge, none of the patients on whom we have performed the GNB have returned to the ED for recurrent pain. Therefore, the GNB might also provide the appropriate bridge from ED care to outpatient follow-up, thereby reducing the need for patients to return to the ED for recurrent pain.

2.3.3 Assessment of Potential Risks and Benefits

The GNB is low risk and has an excellent safety profile given the distal, superficial, and terminal location of the nerves and lack of major arteries. There have been no published reported complications of this block and in our anecdotal experience none of our patients have experienced complications from the GNB. To minimize the risk of theoretical complications and risks, we will take the following precautions.

- Utilize use 80% of ideal body weight (actual body weight dosing for patients with BMI less than 25 kg/m^2) dosing to minimize the risk of toxic effects and LAST
- Utilize a dilute concentration (as described above) to allow for longer injection time, thereby allowing prompt identification of any signs of symptoms of toxicity which can prompt immediate termination of further injection
- Aspirate prior to administration of each aliquot of anesthetic to further allow for early identification of any signs of symptoms of toxicity
- Utilize direct ultrasound guidance to visualize the needle in relationship to anatomical structures to minimize the risk of damaging nearby structures and the risk of intravascular injection
- Prior to the start of the procedure, all patients will be placed on the cardiorespiratory monitor and will have an updated blood pressure. During the procedure, their vitals will be monitored for either tachy- or bradyarrhythmia and for at least 30 minutes after (as suggested by ASRA guidelines) after blockade.

- Rescue therapy (20% intralipid) will be immediately available should local anesthetic systemic toxicity occur

Despite these potential risks, bupivacaine and other local anesthetics are very frequently utilized for numerous indications within the scope of emergency medicine, anesthesiology, surgery, and the surgical subspecialties. With these precautions, the risks are far outweighed by the potential benefits in that adequate anesthesia can reduce the need for high doses of potentially harmful opioid anesthetics, which themselves can be associated with several severe adverse effects including but not limited to dependence and tolerance, delirium, nausea and vomiting, and respiratory depression leading to hypoxia and respiratory arrest.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	*ENDPOINTS*	*JUSTIFICATION FOR ENDPOINTS*
Primary		
Pain Reduction To determine whether patients receiving a GNB for knee pain experience greater pain reduction compared to conventional analgesia	Difference in pain level as measured by NRS at pre-intervention (GNB or conventional) and at either 1-hour after enrollment or at time of ED discharge, whichever occurs first (post intervention)	This endpoint will evaluate whether the GNB provides a clinically meaningful reduction in pain compared to conventional analgesia.
Secondary		
Duration of Analgesia To determine whether patients who receive a GNB experience a longer duration of analgesia compared to those who receive conventional analgesia	Difference in duration of analgesia, assessed by a follow-up telephone call at 24-36 hours post intervention	This endpoint will evaluate whether the GNB will result in longer duration of analgesia compared to conventional analgesia.
Patient Reported Outcomes, including Patient Satisfaction To determine whether patients who receive a GNB report higher patient satisfaction compared to those who receive conventional analgesia	Difference in functionality/ satisfaction as measured by the APS-POQ -RED between GNB and conventional analgesia. Questionnaire administered at either 1-hour post enrollment or at time of ED discharge, whichever occurs first.	This endpoint will evaluate whether patients will have improved satisfaction with treatment when receiving the GNB as compared to conventional analgesia using a modified version of the APS-POQ designed for the ED
Reduce ED LOS To determine whether patients who receive a GNB have shorter ED length of stay (LOS) compared to those who receive conventional analgesia	Difference in ED LOS between GNB and conventional analgesia, as determined by time from enrollment in study to time of ED discharge.	This endpoint will evaluate whether treatment with the GNB can shorten ED LOS compared to conventional analgesia

4 STUDY PLAN

4.1 Study Design

This is a prospective, open-label, investigator-initiated, convenience-enrollment, randomized-controlled trial comparing the efficacy of the ultrasound-guided three-point GNB versus conventional analgesia of atraumatic knee pain. Patients who present to the ED with atraumatic knee pain will receive plain film radiography of the knee to evaluate for acute fracture or large knee joint effusion. Patients without radiographic evidence of fracture or large knee joint effusion will be eligible for enrollment. Patients for whom there are concerns for infection, including cellulitis or septic arthritis will be excluded. Other exclusion criteria are listed in Section 5.2. We hypothesize that patients who receive a GNB will experience a greater reduction in pain and longer acting analgesia compared to those managed with conventional analgesia.

Patients who present to one of the four primary ED sites within the Penn Medicine health system (HUP, PPMC, PAH, HUP Cedar) will be eligible for inclusion as participants. Research assistants (RAs), who are present in the ED at HUP and PPMC daily, will assist with recruitment at those sites, and potentially eligible patients at PAH and HUP Cedar will be recruited by participating physicians. The study team will review inclusion and exclusion criteria with the RAs prior to the initiation of patient enrollment. Furthermore, an EPIC Haiku notification will be created to alert the study team of any patient who presents to the ED with knee pain. Prior to recruitment, it is assumed that most patients who will become participants will have been offered conventional oral, intravenous, or topical analgesics as part of their normal treatment regimen. If completion and radiologist read of plain film imaging (1) does not show evidence of acute fracture and (2) does not show evidence of a large knee joint effusion, patients will be screened for eligibility by either an RA or the performing physician. Patients with small or moderate sized effusions will be eligible for inclusion if there is no clinical concern for septic arthritis of the knee. Large effusions will be excluded as this may distort the anatomical and sonographic landmarks for performing the GNB. The physician who performs the GNB for participants may not necessarily be the physician who is primarily caring for the patient clinically in the ED.

Those patients who satisfy all inclusion criteria will be offered enrollment and consented by a participating emergency physician or RA. Upon consenting, patients will be asked to rate their knee pain on the NRS. This initial evaluation is based on the current severity of the pain, regardless of whether patients received any analgesics prior to obtaining radiography. Study will not begin until plain film imaging has been reviewed by a radiologist, at which point patients will be considered for eligibility.

Utilizing a random number generator, patients will be randomized to either the intervention arm (GNB) or the control (conventional analgesia) arm. Within the intervention arm, a three-point GNB will be performed under ultrasound guidance using 80% of ideal body weight (80% of *actual* body weight if BMI is less than 25 kg/m^2) dosing of 0.5% bupivacaine with 4 mg dexamethasone, divided into three separate aliquots (5 mL of 0.5% bupivacaine with 1-2 mg dexamethasone) which will be administered to the SMGN, SLGN, and IMGN. The performing

physician will first identify all landmarks via ultrasound, which include the superomedial and -lateral knee (aligning the probe longitudinally with the femoral condyle) and the inferomedial knee (aligning the probe longitudinally with the tibial condyle). Color doppler will be applied to note any vascular structures within the field of view of injection. The patient will be placed on the cardiopulmonary monitor prior to the GNB. The GNB will be performed via ultrasound guidance in real-time.

The control arm will be treated with oral, intravenous, or topical analgesics, as per the treating clinician's discretion. Patients will be observed on continuous cardiorespiratory monitoring in the ED for at least 30-minutes following treatment to evaluate for treatment effect and adverse events. Patients will be discharged from the ED when their pain is sufficiently controlled, and they are agreeable for discharge. Of note, patients in both treatment arms will be eligible for additional analgesics, as needed, at any point after enrollment. This will be recorded and evaluated during analysis. At either 1-hour after enrollment or at the time of discharge from the ED (whichever occurs first), patients of both treatment arms will be again asked to rate their pain severity on the NRS and asked to complete the modified APS-POQ-RED. This survey will be conducted either by RAs (during daytime hours, if available) or the performing physician (if overnight). Patients will subsequently receive a phone call approximately 24 to 36 hours after the treatment by a member of the study team (performing physician, RA, or the clinical research coordinator (CRC) from the Emergency Ultrasound Division) to evaluate the duration of analgesia. If the block is performed during overnight hours, the follow-up call will take place the next day (between 24 to 36 hours after treatment). After this assessment, the participant's involvement in the study will be concluded. Only in cases where an adverse event occurred that either requires hospitalization or ambulatory follow-up will a participant's participation last longer than 24 hours. All data collected by the RA, the CRC, or the performing physician will be stored in REDCap. The RAs will transmit all research data, including an encrypted medical record number (MRN) and all pain scale responses obtained from the study participants to the Ultrasound Division's CRC, who will be responsible for storing and managing data on REDCap.

Patients with large knee effusions will not be included in the study as large effusions can make the GNB more difficult to perform by distorting the anatomical and sonographic landmarks, and we wish to avoid the additional risk of inadvertent intra-articular injections. In our experience, we have been able to perform the GNB on patients with small and moderate sized effusions without difficulty.

4.2 Scientific Rationale for Study Design

This study seeks to evaluate whether an ultrasound-guided GNB can provide a clinically significant reduction in pain among patients suffering with acute on chronic knee, which in most cases will be attributed to knee OA. Knee OA is very prevalent, and flares of knee OA are a common reason why patients present to the ED, where patients typically receive oral, topical, or intravenous analgesics. However, these therapies are often ineffective for managing

breakthrough knee OA pain. Alternative analgesia strategies, such as the GNB, have shown efficacy in the rheumatology and orthopaedic literature for managing chronic knee OA pain. Development and implementation of safe alternative modes of analgesia may help to effectively manage breakthrough pain associated with knee OA without high doses of opioids or other potentially harmful non-opioid analgesics. Several isolated case reports have demonstrated success in the ED; however, comparative or randomized studies have not evaluated the utility of the GNB among ED patients who present with breakthrough knee OA pain.

4.3 Justification for Dose

For the GNB arm, the maximum recommended dosing for bupivacaine for regional anesthesia is 2.5 mg/kg. To minimize the risk of LAST, we will utilize weight-based dosing at 80% of the maximal safe dosing which will allow for effective and prolonged analgesia while minimizing the risk of complications and LAST. Patients with body mass index (BMI) greater than 25 kg/m^2 will receive a total of 80% of their ideal body weight dosing in bupivacaine. Patients with a BMI of equal to or less than 25 kg/m^2 will receive a total of 80% of their actual body weight dosing in bupivacaine. This total amount will be divided into three equal aliquots that will be injected around the three genicular nerves), which will would be well below the recommended maximal dose for both female and male patients. Dexamethasone dosing ranging from 4-8 mg has shown to prolong regional anesthesia by the prevention of enzymatic processing of local anesthetics, and is commonly used as an adjuvant in both the perioperative setting and in the ED. Given the relatively low volume and dose of anesthetic that will be administered, we plan to supplement the blocks with 4 mg dexamethasone, divided equally into the three injections.

4.4 End of Study Definition

A participant will have completed this study at 24 to 36 hours after blockade, when the research assistant or performing physician will contact the patient via telephone for follow-up assessment, to evaluate for duration of analgesia. For patients that experience an adverse event that requires admission to the hospital or ambulatory follow-up, their participation in the study might be extended beyond 24 to 36-hours as these adverse events and outcomes will be tracked.

Patients who receive the GNB and rate their pain on the NRS before and after the procedure, even those who refuse the APS-POQ-RED survey responses and who are not available to be reached by phone the next day, will still be included in the data analysis for the primary and one secondary endpoint (pain levels, LOS).

5 STUDY POPULATION

5.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all the following criteria:

1. Patient presenting to ED with atraumatic knee pain
2. Provision of signed and dated informed consent form and stated willingness to comply with all study procedures and availability for the duration of the study
3. Equal to or over the age of 18 years
4. Have plain film radiography of the knee obtained during the encounter
5. Pain measured on NRS between 5 and 10

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Fracture or dislocation on plain film imaging
2. Large knee joint effusion identified on plain film imaging
3. Allergy to bupivacaine or local anesthetics, contraindication to local anesthetics (e.g., G6PD deficiency), or history of LAST after receiving anesthetics.
4. Pregnancy
5. Incarcerated
6. History of ipsilateral partial or total knee arthroplasty (patients with previous knee surgeries that are unrelated to the joint, e.g., arthroscopy, ligamentous repair will be eligible)
7. Clinical or radiographic concern for infection (e.g., septic joint)
8. Hemodynamic instability
9. Altered mental status or inability to consent for the procedure

Justification of selected inclusion and exclusion criteria:

- Large knee effusion on x-ray: Patients with large knee effusions will not be included in the study as large effusions can make the GNB more difficult to perform by distorting the anatomical and sonographic landmarks, and we wish to avoid the additional risk of inadvertent intra-articular injections. In our experience, we have been able to perform the GNB on patients with small and moderate sized effusions without difficulty. Given that many patients with knee OA and chronic knee pain have small to moderate knee

effusions, including them in this study would provide a more accurate representation of the population suffering with chronic and acute on chronic knee pain.

- Patients <18 years old: pediatric patients typically do not suffer from knee OA
- Pregnant patients have decreased levels of alpha-1 glycoprotein which places them at inherently increased risk for LAST.
- Incarcerated patients will be difficult to follow up with and we will not be able to obtain 2 of the 3 secondary endpoints on these patients.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 Strategies for Recruitment and Retention

Patients presenting to the EDs of HUP, PPMC, PAH, or HUP Cedar with knee pain for whom plain film imaging has been obtained will be screened by a member of study team to determine eligibility based on inclusion and exclusion criteria described in sections 5.1 and 5.2. If the patient is eligible, a member of study team will approach the patient to obtain informed consent.

- Target sample size: 17 patients in both the intervention and control treatment arms
- Anticipated accrual rate: 100%
- Anticipated number of sites and in which participants are to be enrolled: 4 clinical sites (EDs of HUP, PPMC, PAH, or HUP Cedar)
- Source of participants: ED patients
- Recruitment venues: ED
- How potential participants will be identified and approached: (1) Potentially eligible patients under the care of a participating physician will be identified and approached

during the usual course of care. (2) Potentially eligible patients who are not under the direct care of a participating physician will be identified by chart screening and direct communication with the primary physician by either participating physicians or research assistants.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

The study interventions are either conventional analgesia or a one-time three-point GNB with weight-based 0.5% bupivacaine and 4 mL dexamethasone divided into three separate injections, ~~around the SMGN, SLGN, and IMGN. Bupivacaine and dexamethasone are commercially~~ available and are being used in accordance with approved labeling.

For participants randomized to the GNB arm, pre-procedural ultrasound will be performed to evaluate the target sites of injection (e.g., superomedial femoral condyle, the superolateral femoral condyle, and the inferomedial fibular condyle) on the superomedial, superolateral, and inferomedial aspects of the knee. Color doppler will be used to identify any of the geniculate arteries (superomedial, superolateral, and inferomedial geniculate arteries) which may be present in proximity to their respective genicular nerves. Once the target signs have been obtained; the entire knee will be prepped with chlorhexidine antiseptic and draped in standard fashion. Using sterile conditions (including single sterile gloves), a 5-15 MHz linear ultrasound transducer will be prepared with a sterile ultrasound probe cover and sterile ultrasound gel. The ultrasound will be placed in a cephalad to caudad direction with the probe indicator facing cephalad, and color doppler will be always on during the procedure for real time visualization of potential vasculature. For each injection, a separate needle will be used to minimize the risk of infection. In most cases, we will use 1.5-inch 20 or 22-gauge hypodermic needles, however for patients with larger body habitus requiring more depth and a longer needle, a 20- or 22-gauge 3.5-inch Quincke spinal needle will be used. For the superomedial and superolateral blocks, the needle will be introduced from a cephalad to caudad direction (toward the knee) and for the inferomedial block, the needle will be advanced from a caudad to cephalad direction (toward the knee). In all cases, the needle will be advanced toward the periosteum under constant visualization, taking care to avoid any potential vascular structures. Once the needle contacts the periosteum, aspiration will be performed to ensure the needle tip is not within a vascular structure, at which time a small aliquot of anesthetic will be injected to lift the muscle off the periosteum and periosteal fat pad. Once proper lifting has been visualized, the remainder of anesthetic will be slowly administered over the span of 30-seconds while maintaining sonographic visualization of the needle tip. Upon deposition of anesthetic at each site, the needle will be removed, and the site of skin puncture will be covered with a taped piece of gauze or bandage.

Participants randomized to conventional analgesia, will be treated with standard medication(s) which include any oral, topical, or intravenous analgesic, including but not limited to acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), lidocaine patches, opioids. These are all commercially available, many of which available over the counter, and are being used in accordance with approved labeling.

No experimental agents are being used in this study. No experimental off label devices are being used in this study.

6.1.2 Dosing and Administration

For the GNB arm, dosing is determined based on ideal body weight such that the total amount of bupivacaine will fall well under the maximum recommended dosing by weight (2.5 mg/kg ideal body weight). In this case, 80% of ideal body weight-based (actual body weight for patients with BMI less than 25 kg/m^2) dosing of 0.5% bupivacaine (as previously described) and 4 mg dexamethasone, divided into three injections around the affected knee, one each around the SMGN, SLGN, and IMGN. Administration of each injection will occur over the span of one minute to monitor for potential adverse effects to ensure the maximal degree of safety. If any signs or symptoms of LAST occur (e.g., tachy- or brady-dysrhythmias, hyper- or hypotension), or if a patient reports subjective feelings of dizziness, confusion, or tingling (including perioral or tongue paresthesia), the injection will be halted immediately. Participants will be instructed to immediately alert the physician if any of these symptoms occur.

There is a precaution issued by the FDA regarding use of bupivacaine in geriatric patients specifically stating that "Clinical studies of bupivacaine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range." While this is not contraindicated in geriatric patients, caution is recommended as elderly patients may have age-related physiological changes that can affect the pharmacokinetics and pharmacodynamics of bupivacaine including decreased metabolism and reduced plasma protein binding. Therefore, it is recommended to utilize dosing at less than maximally recommended doses and monitor closely for adverse effects. To minimize these risks, we are utilizing 80% of their ideal body weight dosing of bupivacaine. Furthermore, all patients will be monitored in the ED for at least 30 minutes after the block. Should an adverse event occur, reversal therapy will immediately be available (see Section 6.5 for details).

The GNB will be performed under clean conditions (e.g., sterile gloves, chlorhexidine skin prep that will be allowed to completely dry before puncturing the skin) and under ultrasound guidance.

For the control arm, conventional anesthetics will be dosed at the discretion of the primary provider caring for the patient and will include standard dosing of medications. This includes but is not limited to: 1) oral acetaminophen 325 mg to 975 mg, 2) oral ibuprofen 400 mg to 600 mg, 3) intravenous ketorolac 15 mg to 30 mg, 4) topical 5% lidocaine patches, 5) oral oxycodone 5 mg to 20 mg, 6) intravenous morphine 0.05 mg/kg to 0.1 mg/kg, or 7) intravenous hydromorphone 0.015 mg/kg to 0.03 mg/kg.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

For the GNB arm, bupivacaine 0.5% is a commonly used medication in the ED. The participating physician will obtain this medication as they would during typical interventions. Briefly, the participating physician will order the bupivacaine and dexamethasone with specific instructions to nursing to hold and provide the medications (in their commercially available storage vials) to the participating physician. Clinical pharmacists will approve the ordered medications, after which nursing will retrieve the medications from the secured drug rooms (i.e., Omnicell) and directly hand the unopened vials to the participating physician.

For the control arm, the participating physician will order conventional analgesic medications as they normally would, at which time nursing would retrieve the medications and administer them to the patients in accordance with electronic orders.

6.2.2 Formulation, Appearance, Packaging, and Labeling

For the GNB arm, bupivacaine 0.5% is stored in either the Omnicell (immediately available medication storage within the emergency department) or central pharmacy, where it can be sent down to the ED. The medication is stored at room temperature in individually sealed vials. No preparation other than drawing up the medication with a needle and syringe will be necessary, which will be the responsibility of the participating physician administrating the GNB. Vials are single use and clearly labelled. Bupivacaine will be mixed at the bedside with dexamethasone prior to injection. Bupivacaine on formulary is manufactured by Xellia Pharmaceuticals LLC. Dexamethasone 4mg/mL is also available in the ED Omnicell and commonly utilized in emergency patient care. Bupivacaine 0.5% is distributed by Hospira and dexamethasone sodium phosphate 4mg/mL is distributed by Hikma.

6.2.3 Product Storage and Stability

Bupivacaine 0.5% is stored at room temperature (68F to 77F, per manufacturer drug information sheet) and is relatively stable. Little or no changes in concentration have been observed at four weeks of storage at room temperature.

Dexamethasone phosphate 4 mg/ml is refrigerated (35F-46F) but is stable for 24 hours at 77F. See drug datasheet.

There is a theoretical risk of crystallization when combining certain local anesthetics and dexamethasone. However, this risk is significantly reduced given that we are using bupivacaine as the local anesthetic. Moreover, the formulation of dexamethasone we are using for this study (water soluble dexamethasone sodium phosphate) is compatible with bupivacaine, whereas more lipophilic formulations (dexamethasone palmitate or acetate) have a higher risk of precipitating when mixed with local anesthetics. Nonetheless, the crystals that may be formed are typically less than 10 microns in diameter, which do not pose any clinical risk (Choi 2021). No published

studies to date have demonstrated adverse clinical effects relating to possible crystallization of dexamethasone and local anesthetics.

6.2.4 Preparation

For the GNB arm, bupivacaine 0.5% is available in single-use vials as a ready-to-use liquid. It will be drawn up with a blunt needle and syringe and requires no special preparation prior to administration. In this case, three separate syringes will be loaded with the appropriate volume 0.5% bupivacaine (weight-based dosing as described above). To each syringe, 1-2 mg of dexamethasone will be added to the bupivacaine (for a total of 4 mg of dexamethasone).

Preparation of medications for the control arm will be prepared and administered to the patient by nursing as per the electronic orders, as is standard of care.

6.3 Measures to Minimize Bias: Randomization and Blinding

Participants will be randomly assigned to either the intervention arm (GNB) or standard-of-care (control) arm using a commercially available random number generator. Patient consent will explicitly state that they will be randomized into either treatment arm. As this is an open-labeled trial, there will be no blinding of intervention to participants, performing physicians, or research assistants.

6.4 Study Intervention Compliance

Protocol adherence will require the participant to initially rate their pain on the NRS then to receive either the GNB (intervention arm) or standard-of-care therapy (control arm). At either 1-hour post enrollment or time of discharge from the ED (whichever occurs first), protocol adherence will require the participant to rate their pain on the NRS and complete the APS-POQ-RED questionnaire. At 24 to 36 hours after treatment, participants will be contacted by the performing physician or research assistant to evaluate duration of analgesia received in the ED.

Administration of the trial drugs will be documented (unblinded) in the electronic medical record (PennChart, Epic) as administered medications. These will similarly be documented by the participating physician or research assistant in REDCap. Similarly, medications administered prior to study initiation and medications administered to the control arm and any additional medications administered after treatment will be documented in the electronic medical record (PennChart, Epic) as administered medications as well as in REDCap by the participating physician or a research assistant. Clinical outcome data will be documented in REDCap by the participating physician or a research assistant.

6.5 Concomitant Therapy

For the GNB arm, in addition to bupivacaine, the GNB will be augmented with adjuvant dexamethasone (4 mg divided into three aliquots). Dexamethasone is commonly used in the

perioperative setting by regional anesthesiologists and in the ED to extend the duration of regional anesthesia (Fernández Martin 2023).

6.5.1 Rescue Medicine

For the GNB arm, if signs or symptoms of LAST were to develop at any point during administration of the intervention drug or after administration, patients will be assessed for the need for rescue medications. At all study sites, benzodiazepines and lipid emulsion therapy will be available and administered if deemed necessary by the performing physician (Shalaby 2024). For seizures, a benzodiazepine such as midazolam or lorazepam will be administered as per established dosing guidelines. Intralipid will be administered as per institutional guidelines to help reverse LAST. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication will be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

The intervention in this study is a one-time three-point GNB performed with bupivacaine and dexamethasone. Moreover, both prior to and after the intervention, patients will continue to receive analgesia as needed in accordance with standard of care (e.g., a patient receives a GNB but still has significant pain 60-minutes afterward will be offered additional conventional analgesics, at the discretion of the primary physician).

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

7.3 Lost To Follow-Up

A participant will be considered lost to follow-up if he or she does not respond via telephone at the 24-hour follow-up after three attempts by the participating emergency physician or clinical research assistant. However, patient intervention and any outcome data that has previously been obtained (e.g., data collected at time of discharge from the ED) will still be included. All participants who complete the initial assessment by the time of discharge will be included in the analysis. No follow-up visits will be required.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Efficacy Assessments

Patients presenting to the ED of one of the four study locations (HUP, PPMC, PAH, HUP Cedar) with knee pain attributed to knee OA with plain film radiography who are eligible for enrollment based on the inclusion and exclusion criteria described in sections 5.1 and 5.2 will be approached by a member of the study team to obtain informed consent.

Prior to randomization, a pain score will be obtained using the NRS by the performing physician. Patients will be randomized to either the intervention arm (GNB) or the control arm, at which point they will receive treatment. At either 1-hour after enrollment or at time of discharge from the ED (whichever occurs first), the performing ED physician, or research assistant will ask the patient to rate their pain severity on the NRS. At that same time, a member of the study team will also have the patient complete the APS-POQ-RED. At 24 to 36-hours after treatment, a clinical research assistant or the treating emergency physician will contact the patient to obtain follow-up assessment and duration or analgesia.

8.2 Safety and Other Assessments

Patients will have a set of vital signs obtained prior to initiation of treatment and after 30 minutes of treatment. During this time, patients will be observed in the ED. Either the treating physician who performed the intervention or the CRC will follow up with patients via phone call 24 to 36 hours after the procedure to determine the presence of complications.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.

8.3.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of either the investigator or the sponsor, is:

- fatal
- life-threatening

- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
- required intervention to prevent permanent impairment or damage (for devices only)

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

8.3.3 Unanticipated Adverse Device Effect (UADE)

Not applicable.

8.3.4 Classification of an Adverse Event

8.3.4.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.4.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to <study intervention> assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be considered.

- Related – The AE is known to occur with the GNB, there is a reasonable possibility that the GNB caused the AE, or there is a temporal relationship between the GNB and event.

Reasonable possibility means that there is evidence to suggest a causal relationship between the GNB and the AE.

- Not Related – There is no temporal relationship between the GNB and event onset, or an alternate etiology has been established.

8.3.4.3 Expectedness

The medical director, Dr. Michael Shalaby, will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the GNB.

8.3.5 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by monitoring and recording potential adverse effects using the Common Terminology Criteria for Adverse Events (CTCAE) at each study visit. Participants will be monitored by medical histories, physical examinations, and vital signs. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the subject, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (CTCAE Grade 1-5)
2. Duration (start and end dates)
3. Relationship to the study treatment or process – [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment or process – [Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol].
5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.3.6 Adverse Event Reporting

Reporting Period

Adverse events will be reported from the time of informed consent until study completion.

Investigator Reporting: Notifying the Study Sponsor

Not Applicable.

Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

8.3.7 Serious Adverse Event Reporting

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered GNB related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the GNB caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the GNB and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

8.3.8 Reporting Events to Participants

Any expected adverse events are anticipated to occur within the first 30 minutes of the GNB, such that all participants will be monitored during that time in person. Any concerns of potential adverse events will be communicated to participants at this time.

8.3.9 Events of Special Interest

Not applicable.

8.3.10 Reporting of Pregnancy

Not applicable.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problem Reporting

Unanticipated problems (UPs) such as:

- Post-marketing withdrawal of a drug, device, or biologic used in a research protocol due to safety concerns.
- FDA ban of a drug, device, or biologic used in a research protocol due to safety concerns.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study
- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.)

should be reported by the investigator to the medical director. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported as any other SAE.
- Any other UP will be reported to the IRB and to the DCC within 48 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 48 hours of the IRB's receipt of the report of the problem from the investigator.

8.4.3 Reporting Unanticipated Problems To Participants

Not applicable.

8.5 Device Reporting

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Primary endpoints:

- H_0: Mean change in pain levels pre / post GNB = Mean change in pain levels pre / post conventional therapy
- H_1: Mean change in pain levels pre / post GNB ≠ Mean change in pain levels pre / post conventional therapy

Secondary endpoints:

- H_0: Mean duration of analgesia for patients receiving GNB = Mean duration of analgesia for patients receiving conventional therapy
- H_1: Mean duration of analgesia for patients receiving GNB ≠ Mean duration of analgesia for patients receiving conventional therapy
- H_0: Mean APS-POQ-RED score for patients receiving GNB = Mean APS-POQ-RED score for patients receiving conventional therapy
- H_1: Mean APS-POQ-RED score for patients receiving GNB ≠ Mean APS-POQ-RED score for patients receiving conventional therapy
- H_0: Mean ED LOS for patients receiving GNB = Mean patient satisfaction for patients receiving conventional therapy
- H_1: Mean ED LOS for patients receiving GNB ≠ Mean patient satisfaction for patients receiving conventional therapy

9.2 Sample Size Determination

To determine the number of patients needed in each study arm for sufficient sample size we considered the primary outcome of change in pain levels pre/post treatment as measured by the NRS as this was the largest sample size needed to detect a clinically meaningful effect.

The sample size was loosely based on an RCT by Shanahan et al. 2023, for which the mean change in the visual analog scale (VAS: 0-10 scale) from baseline at 2 weeks was 3.5 (GNB) and 0.7 (sham injection group). Assuming the mean change in NRS pain score pre/post treatment between the GNB and standard analgesia (difference in difference) will be smaller in a shorter period of time, group sample size of 17 (each group) will achieve 80% power to detect a difference in NRS between treatment arms as small as 1.6, with alpha set at 0.05 and standard deviation of differences set at 2.0 using a two-sided two-sample equal-variance t-test with a 5-10% loss to follow-up at the 24 hour mark.

9.3 Populations for Analyses

All patients who are enrolled and receive either the GNB or conventional analgesia as part of the study will be included in the analysis dataset.

9.4 Statistical Analyses

9.4.1 General Approach

Prior to analysis, all primary and secondary outcome measures will be summarized with descriptive statistics (mean ± standard deviation (SD) or median and IQR), their distributions examined, tested for normality and transformed using log base 10 as needed. Additionally, all

demographics will be summarized using mean ± SD or median and IQR, for continuous variables and frequencies and percentages for categorical variables. Results from statistical testing for continuous variables, will be presented with p-values and 95% confidence intervals for tests using means or medians and IQR if a non-parametric test is used. For categorical variables, the chi-square or Fisher's exact test will be performed to examine whether treatment arms differ with regard to demographics and other baseline variables. Similarly, for side effects, descriptive statistics and Fisher's exact tests will be performed for possible differences between the treatment arms. Regardless of type statistical test, all will be two-sided.

The primary efficacy endpoint is change in pain level as measured on the NRS at baseline (pre intervention) and at post intervention (either 1-hour post-enrollment or at time of ED discharge, whichever occurs first) in both treatment arms. The NRS is an ordinal variable, measured on a 0-10 scale and will be treated as a repeated measure. To determine differences in pain level between GNB and conventional analgesia treatment arms, a 2-factor analysis of variance in repeated measures will be performed where treatment arm is the grouping factor and time (pre/post) is the repeated measure. To adjust for multiple comparisons, post-hoc pairwise Tukey-Kramer tests will be performed. Results will be presented as means ± 95% confidence intervals for each treatment arm/time point. Shapiro-Wilkes test will be used to test for normality. If not normally distributed, data will be transformed using log base 10 transformation. If missing time points, analysis type will change to a mixed general linear model where treatment arm is a fixed factor and time is random.

9.4.2 Analysis of the Secondary Endpoint(s)

Two secondary endpoints to be measured are length of time until additional analgesia needed after initial treatment (GNB or conventional analgesia) and ED LOS. Both of these endpoints are interval/ratio variables measured in hours. Additional analgesia time will be assessed at 24-36 hours after intervention by phone call or EMR if still in the ED or admitted to the hospital. ED-LOS will be assessed by EMR chart review. To assess differences between treatment arms for both these time endpoints, either a 2-sample t-test (normally distributed) or a Wilcoxon rank-sum test (positively skewed) will be performed.

The final secondary endpoint is the 6 questions on the modified APS-POQ-RED administered . Each of 5 questions are on an ordinal scale from 0-10. For each question, a 2-sample t-test will be performed.

9.4.3 Safety Analyses

Adverse events will be coded as previously described and Section 8. Safety analyses will be reported and presented as summary statistics. For side effects, descriptive statistics and Fisher's exact tests will be performed for possible differences between the treatment arms.

9.4.4 Baseline Descriptive Statistics

All demographics will be summarized using mean ± SD, for continuous variables and frequencies and percentages for categorical variables. Standard statistical tests (chi-square and 2-sample t-tests or Wilcoxon rank-sum test) will be performed to examine whether patients differ with regard to demographics and other baseline variables in the 2 study arms.

9.4.5 Planned Interim Analyses

An interim analysis of the primary and secondary endpoints will be conducted after the enrollment of 30 patients, with 15 patients in each arm. This analysis will assess the data collected up to that point to ensure the study's integrity and to make any necessary adjustments based on the findings.

9.4.6 Sub-Group Analyses

None.

9.4.7 Tabulation of Individual Participant Data

Individual patient data will be listed by endpoint of pain rating on NRS at either 1-hour after enrollment or at time of discharge from the ED (whichever occurs first), via pain questionnaire administered at at that same time, and duration of analgesia (which will be assessed during a follow-up phone call performed by a research assistant) at 24 to 36 hours after enrollment.

9.4.8 Exploratory Analyses

None.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the GNB, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering GNB. The following consent materials are submitted with this protocol: **Informed Consent Form**.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the Sponsor or the PI at any site if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All discussions with potential participants, including by not limited to recruitment, consent discussion, and the study procedures will occur in private rooms behind closed doors within the emergency department.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on REDCap. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on REDCap.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored on REDCap. After the study is completed, the de-identified, archived data will be on REDCap for use by other researchers including those outside of the study. Permission to store data on REDCap will be included in the informed consent.

When the study is completed, access to study data and/or samples will be provided through REDCap.

10.1.5 Safety Oversight

Safety oversight will be under the direction of the PI and centralized monitoring group consisting of the Division of Ultrasound in the Department of Emergency Medicine. As this is a minimal risk study, a Data and Safety Monitoring Board is not planned for this study.

10.1.6 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Centralized monitoring of this study will be completed by the Division of Ultrasound in the Department of Emergency Medicine, including a statistician, five faculty members, five fellows, and a research coordinator. The monitoring will occur once every two months and will consist of a random review of the data for verification of endpoint and safety.
- Independent audits may be conducted by the Office of Clinical Research at the University of Pennsylvania to ensure monitoring practices are performed consistently across all participating sites.

10.1.7 Quality Assurance and Quality Control

All monitoring and audits are to be performed according to ICH GCP E6(R2).

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, and specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 Data Handling and Record Keeping

10.1.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in REDCap and follow ALCOAC standards (attributable, legible, contemporaneous, original, accurate, and complete).

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the phrenic nerve block. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect subject safety; OR

- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the subject's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

10.1.10 Publication and Data Sharing Policy

This study will comply with the data sharing agreement.

The Sponsor must approve all sharing of information/data prior to its occurrence.

10.1.11 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Additional Considerations

Not applicable.

10.3 Protocol Amendment History

Version	*Date*	*Description of Change*	*Brief Rationale*
2.0	5.16.2025	First IRB review	

Version	*Date*	*Description of Change*	*Brief Rationale*

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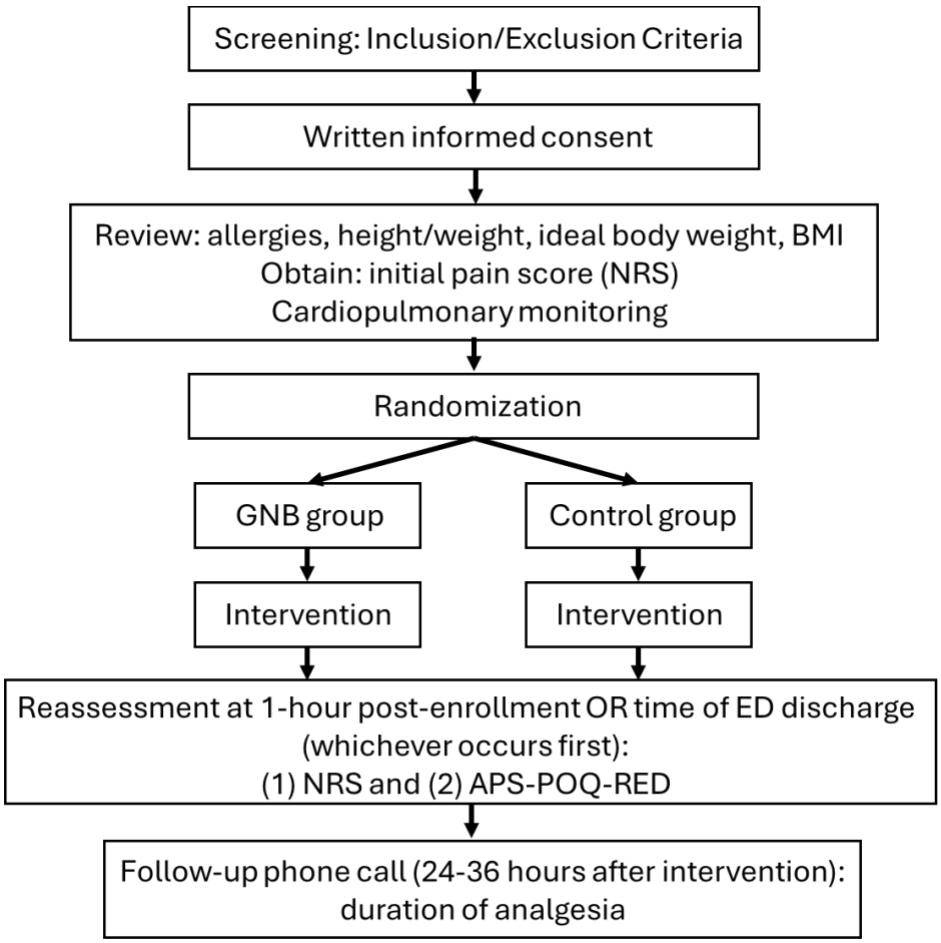
12 APPENDIX

12.1 Schedule of Activities (SoA)



12.2 The American Pain Societies – Patient Outcome Questionnaire Revised for the Emergency Department (APS-POQ-RED)

The following question is about the pain you experienced during your stay in the emergency department:

- On this scale, please tick the current pain you have after treatment in the emergency department (from "0" = no pain to "10" = worst possible pain).

Tick the one number below that describes how your current pain interferes with or prevents you from different activities (from "0" = no did not interfere to "10" = completely interfered).

- During activities in bed such as turning, sitting up, repositioning:
- During activities out of bed such as walking, sitting in a chair, standing:

On this scale, please tick the number describes how your current pain causes you to feel different emotions (from "0" = not at all to "10" = extremely)

- Anxious
- Frightened
- Helpless

In the emergency department, how much pain relief did you receive?

- Please tick the percentage that best shows how much relief you have received for all your pain treatments combined.

This question asks about your overall satisfaction with your pain control.

- Tick the number that best shows how satisfied with the results of your pain treatment in the emergency department (from "0" = extremely dissatisfied to "10" = extremely satisfied)

Modified from:
Hughes JA, Hazelwood S, Lyrstedt AL, Jones L, Brown NJ, Jarugula R, Douglas C, Chu K. Enhancing pain care with the American Pain Society Patient Outcome Questionnaire for use in the emergency department (APS-POQ-RED): validating a patient-reported outcome measure. BMJ Open Qual. 2024 Mar 5;13(1):e002295. doi: 10.1136/bmjoq-2023-002295.

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