CLEVELAND CLINIC
ANESTHESIOLOGY INSTITUTE
DEPARTMENT OF OUTCOMES RESEARCH

A randomized controlled trial to determine the effect of gabapentin enacarbil on opioid consumption and pain scores in patients having hip and knee arthroplasties with spinal anesthesia

Xenoport Protocol: XP-IIT-0033 - **:** Version 7.0; February 26th, 2018

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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[PAGE TO BE PRINTED AND SIGNED WITH EACH FINAL PROTOCOL VERSION]

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ABBREVIATIONS

[Abbreviations or acronyms frequently used in the protocol]

FDA	=	Food and Drug Administration
CRF	=	Case Report Form
IRB	=	Institutional Review Board
AE	=	Adverse Event
SAE	=	Serious Adverse Event
BID	=	twice a day
Pre op	=	preoperative
Post op	=	postoperative
AM/am	=	in the morning
PO	=	by mouth
BIS	=	bispectral index
GA	=	general anesthesia
POD	=	postoperative day
PACU	=	post anesthesia care unit
EPIC	=	electronic privacy information center
REDcap	=	Research Electronic Data Capture (Cleveland clinic internal database)
PCA	=	Patient controlled Analgesia
NRS	=	Numerical rating scale
GEn	=	Gabapentin enacarbil

CONTENTS

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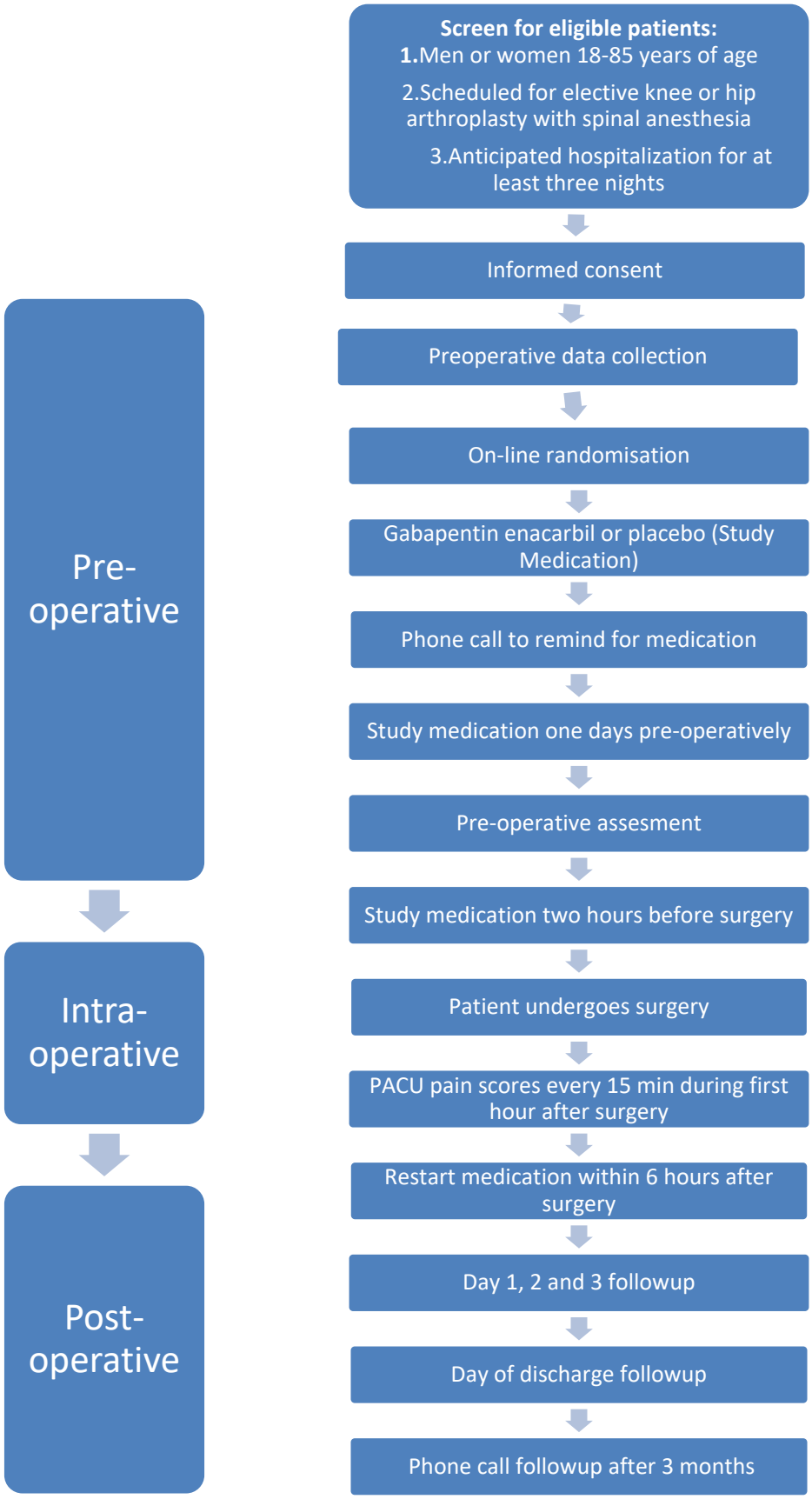
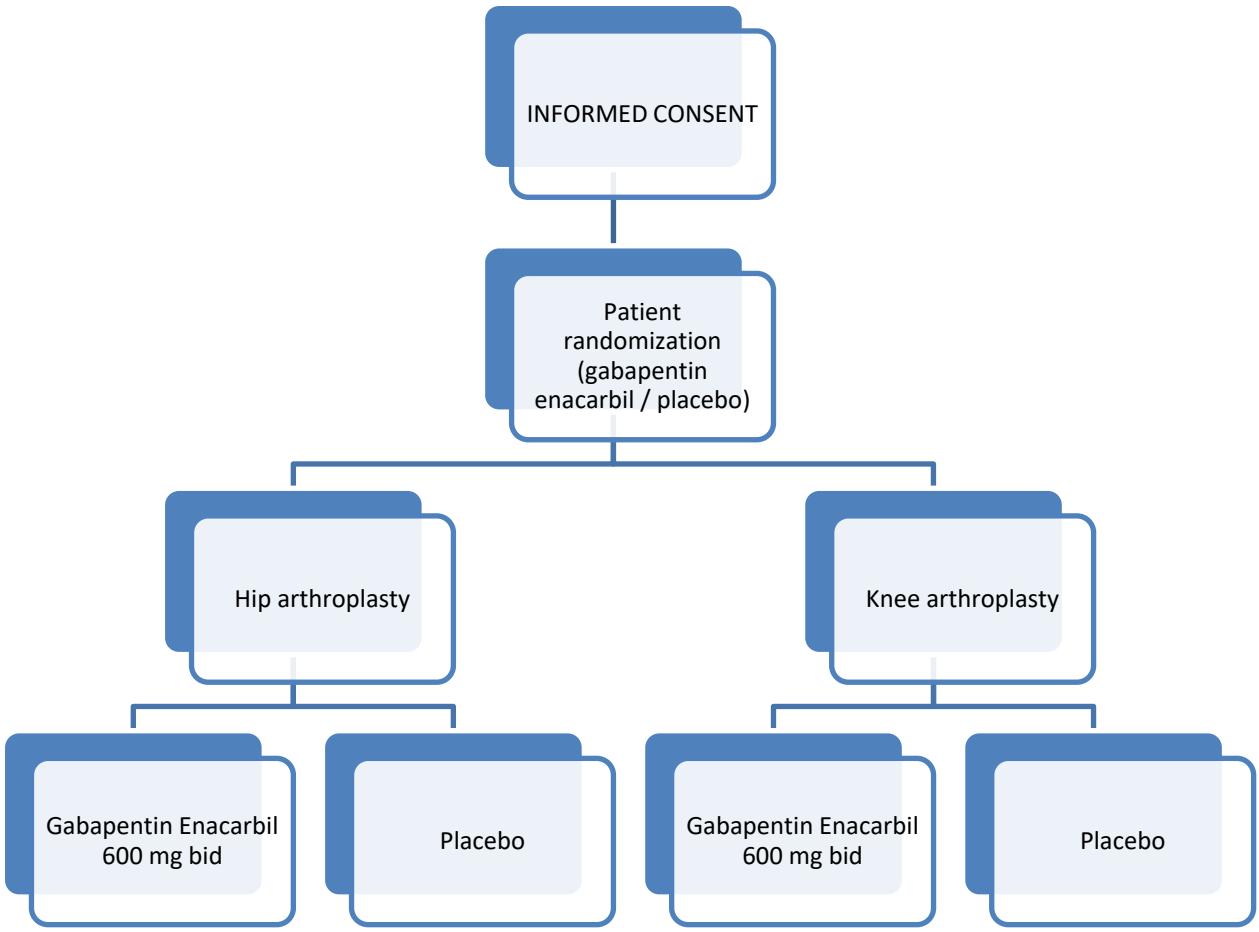
RESEARCH SCHEMA

Title	**A randomized controlled trial to determine the effect of gabapentin enacarbil on opioid consumption and pain scores in patients having hip and knee arthroplasties with spinal anesthesia**
Short Title	**PAIN ATTENUATION IN SURGICAL PATIENTS**
Principal Investigator	**Sabry Ayad, MD**
Primary Objectives	**To assess whether gabapentin enacarbil decreases pain and/or opioid requirements after hip or knee surgery**
Secondary Objectives	**- To assess whether gabapentin enacarbil decreases the incidence of persistent incisional pain three months after surgery when used as a modality of pre-emptive analgesia.** **- To evaluate whether gabapentin enacarbil decreases nausea and vomiting during the initial 72 post-operative hours.** **- To evaluate whether gabapentin enacarbil reduces the duration of hospitalization.** **- To evaluate whether gabapentin enacarbil improves patient's satisfaction**
Study Design	**A randomized, double-blind, placebo-controlled, single institution trial**
Inclusion Criteria	**1. Men or women 18-85 years of age.** **2. Scheduled for elective total primary knee or total primary hip arthroplasty with spinal anesthesia**.
Exclusion Criteria	**1. Creatinine >1.50 mg/dl.** **2. History of clinically important current depression or currently on any prescribed anti-depressant medication.** **3. Previously enrolled in any Xenoport trial.** **4. Use of gabapentin or gabapentinoids (Lyrica, Horizant, Neurontin or Gralise) with one month.** **5. Allergy to gabapentin or gabapentinoids (Lyrica, Horizant, Neurontin or Gralise).** **6. Women who are pregnant or breastfeeding.** **7. History of seizure disorder within the last one-year or taking medications for seizur**
Expected Sample Size	**100 Patients**
Statistical Methodology	**We will consider gabapentin enacarbil group better than placebo group on the postoperative pain management if gabapentin enacarbil group is found noninferior (i.e., not worse) on both outcomes and superior on at least one of the outcomes. We define the a-priori noninferiority pain score delta as 1 point and the opioid delta as**

	1.1 for the ratio in geometric means IV morphine equivalent doses (meaning 10% difference between group's median doses).


Pre-operative
Intra-operative
Post-operative
Screen for eligible patients:
1.Men or women 18-85 years of age
2.Scheduled for elective knee or hip arthroplasty with spinal anesthesia
3.Anticipated hospitalization for at least three nights
Informed consent
Preoperative data collection
On-line randomisation
Gabapentin enacarbil or placebo (Study Medication)
Phone call to remind for medication
Study medication one days pre-operatively
Pre-operative assesment
Study medication two hours before surgery
Patient undergoes surgery
PACU pain scores every 15 min during first hour after surgery
Restart medication within 6 hours after surgery
Day 1, 2 and 3 followup
Day of discharge followup
Phone call followup after 3 months


INFORMED CONSENT
Patient randomization (gabapentin enacarbil / placebo)
Hip arthroplasty
Knee arthroplasty
Gabapentin Enacarbil 600 mg bid
Placebo
Gabapentin Enacarbil 600 mg bid
Placebo

1. INTRODUCTION

1.1 Background

Pain control

Hip and knee replacements are the most common elective surgeries in the U.S.A. Pain control after surgery remains challenging despite advances in surgical techniques and new treatment modalities (32-33). Three-quarters of surgical patients in the United States experience postoperative pain and are unsatisfied with their analgesia (28-29). The major cause of pre-operative anxiety in any surgical patient is fear of postoperative pain (18). Pain is a psychological sensory experience, which is caused by various factors. Surgery results in tissue damage which leads to postoperative pain. Studies in recently developed animal models of postoperative pain have advanced our knowledge of the mechanisms of pain resulting from surgical incision and associated tissue injury.

Post-operative pain has numerous etiologies and many contributing factors; it thus usually responds best to multimodal approaches (28-29). Pain may result from tissue trauma secondary to stretching and compression or direct nerve injury as a result of surgical incisions and burns (1-6). Pain is aggravated by coughing, sneezing, moving etc. or any other movement, which increases pressure over the surgical area. Most clinicians consider nerve blocks to be the optimal approach, but many patients nonetheless require opioids.

Ineffective pain control results in increased mortality and morbidity (7-8, 22). For example, surgery provokes immune depression, which may have deleterious effects. Reducing postoperative pain may speed mobilization and reduce pulmonary and cardiac complications, whereas early mobilization reduces the risk of deep vein thrombosis. This implies that, if post-operative pain is treated effectively, then costs of care could be decreased significantly.

1.2 Gabapentin enacarbil

Gabapentin is an analog of gamma-aminobutyric acid. It is currently approved by the US Food and Drug Administration for treatment for post herpetic neuralgia and seizure disorders. It binds to alpha-2 delta subunit of presynaptic P/Q voltage gated calcium channels, which regulate the release of excitatory neurotransmitters from nociceptive receptors (4). Gabapentinoids can decrease post-operative pain by regulating glutamate release through the calcium channels and also through activation of inhibitory noradrenergic pain pathways in the spinal cord and brain. Gabapentin is absorbed through the duodenum, only minimally protein bound and renally excreted. Antacids interact with gabapentin to impair its absorption.

Gabapentin reaches peak plasma concentrations about two hours after oral administration, and its half-life is between 4.8-8.7 hours; hence, it is given in two daily doses. Since gabapentin is renally excreted, the dose should be reduced in patients with renal dysfunction, especially when creatinine > 1.50 mg/dl (15-16). Side effects include sedation, dizziness, headache, visual disturbances, and peripheral edema (17).

Peri-operative use of gabapentin reduces early post-operative pain and opioid consumption (9-11). Postoperative delirium a complication of general anesthesia is less common after gabapentin administration (24). In 2012, Mahdi Panah Khahi et al compared visual analog scores and fentanyl use in patients given gabapentin pre-operatively and immediately post-incision via nasogastric tube. Patients given gabapentin preoperatively had lower visual analog scores and required less fentanyl than those given the drug later (30).

In another study, less morphine was required in patients given gabapentin both pre- and post-operatively than just pre-operatively. A knee-flexion test was used to check the efficacy of post-operative gabapentin on post-operative pain, which revealed better flexion in patients using both pre- and post-operative gabapentin (12). In a qualitative and quantitative review in patients who had abdominal hysterectomy and spinal surgery, gabapentin decreased pain scores, use of narcotics and symptoms like nausea and vomiting when given pre and peri-operatively(31,34).

A study by Panah Khahi et al revealed that pre-emptive use of gabapentin reduced pain scores on both post-operative day 1 and day 2 and use of opioids in orthopedic patients undergoing internal fixation of tibia (13). Using high dose gabapentin (600 mg) lead to lower pain scores than low dose 300 mg in patients who had lumbar discectomies. Similarly, preemptive use of 600 mg gabapentin orally in patients undergoing abdominal hysterectomies required low amounts of analgesic and antiemetics (14, 20, and 23).

1.3 Clinical Data to Date

Multimodal approach

Opioids are effective analgesics, but cause side effects including sedation, respiratory depression, hypotension, nausea, and constipation. Hence, opioids are often combined with local anesthetics, non-steroidal anti-inflammatory drugs (NSAIDS), acetaminophen, ketamine, or other agents in an effort to reduce postoperative pain while minimizing side effects, an approach termed "multi-modal analgesia" (25-27). NSAIDs are antipyretic and anti-inflammatory, but provoke surgical and gastrointestinal bleeding; renal impairment and they also impair bone healing. The main goal is to decrease opioid use and consequently decrease the incidence of opioid related side effects. Non-opioid analgesics used in this are generally insufficient to treat postoperative pain by themselves, but have substantial opioid sparing effects and thus presumably reduce opioid-related complications.

In summary, opioids provoke numerous severe complications that cause substantial patient morbidity. They also delay discharge from hospital, increase the cost of care, and reduce patient satisfaction.

Multimodal analgesia is believed to decrease length of hospitalization, decrease the cost of care, and shorten recovery (19-21). Multimodal analgesia a decrease opioid use, and hence is thought to indirectly reduce opioid-induced side effects and complications including respiratory depression and ileus. NSAIDS, acetaminophen, ketamine, and pregabalin have been tried in the past as adjuncts to decrease overall consumption of opioids. Acetaminophen is opioid sparing, but must be used cautiously in patients with impaired liver function (35, 36, and 37).

The impact of postoperative opioid related complications is not only important from a clinical perspective, but also from an economic standpoint. The additional cost attributable to opioid side

effects has not been well defined and usually depends on estimates rather than solid data. Our study will provide data to support a full cost-benefit analysis, so the financial benefits of GEn can be concretely evaluated. We thus propose to evaluate the opioid-sparing effect of GEn and, more importantly, the reduction in opioid-related complications.

1.4 Dose Rationale and Risk/Benefits

We would like to test an extended-release formulation of gabapentin enacarbil, a prodrug of gabapentin, a FDA approved drug for post herpetic neuralgia and restless leg syndrome (43). Extended release gabapentin enacarbil and gabapentin are different in their pharmacokinetics and have variable but predictable bioavailability (39). This results in different plasma concentrations at the same doses (39). It is shown to provide dose-proportionality and extended exposure to gabapentin over the range 300 to 6,000 mg (39). At high doses gabapentin transporters in the intestines get saturated, this could be overcome by using an extended release formulation with predictable dose proportional bioavailability (38). GEn is absorbed via high capacity nutrient transporters located throughout the intestinal tract thus providing a predictable dose proportionality and improved bioavailability. A 600 mg dose of gabapentin enacarbil produces at least 312 mg of gabapentin on hydrolysis (39, 40).

A more predictable gabapentin exposure is achieved due to linear relationship of dose-exposure for gabapentin enacarbil and hence the dosing frequency could be decreased (41). Per PI Tmax of gabapentin after 600 mg (Horizant) is 5.0 hours (fasted) and 7.3 hours (fed). GEn provides more sustained dose proportional exposure to gabapentin (unlike gabapentin), which may lead to more predictable exposure with GEn and decreased dosing frequency relative to gabapentin. Due to the mechanism of action of GEn and its predictable bioavailability due to it absorption via the MCT-11 transporters, we would like to prefer GEn to gabapentin.

We thus propose to test the hypothesis that gabapentin enacarbil when used as a modality of pre-emptive analgesia decreases opioid consumption and/or decreases pain scores in hip and knee arthroplasty surgery.

2. STUDY OBJECTIVES

Primary and secondary objectives

The primary objective of this study is to compare the efficacy of gabapentin enacarbil 600 mg BID taken 1 day pre-op and approximately 2 hours before the surgery and restarted within 6 hours of completion of surgery and then 3 days post-operative versus placebo in reducing the use of opiates and/or pain scores in post-hip and knee arthroplasty surgery patients with spinal anesthesia.

Using a randomized design and blinded assessments, our goal is to determine whether Gabapentin enacarbil when used as a modality of pre-emptive analgesia decreased opioid consumption and/or decreased pain scores in hip and knee arthroplasty surgery.

The proposed research will have the following aims:

Primary objectives include:

Primary Aim 1: To assess whether gabapentin enacarbil decreases pain and/or opioid requirements after hip or knee surgery.

Hypothesis: Patients received gabapentin enacarbil will have less pain scores and/or less opioid consumption during the initial 72 hours after hip or knee surgery compared to patients who received placebo, and not worse on either outcome.

Secondary objectives include:

Secondary Aim 1: To assess whether gabapentin enacarbil decreases the incidence of persistent incisional pain three months after surgery when used as a modality of pre-emptive analgesia.
Hypothesis: Gabapentin enacarbil decreases the persistence of incisional pain three months after surgery.

Secondary Aim 2: To evaluate whether gabapentin enacarbil decreases nausea and vomiting during the initial 72 post-operative hours.
Hypothesis: The incidence of postoperative nausea and vomiting is reduced in patients given gabapentin enacarbil during the initial 72 hours after hip and knee replacement surgery.

Secondary Aim 3: To evaluate whether gabapentin enacarbil reduces the duration of hospitalization.
Hypothesis: The duration of hospitalization after knee or hip arthroplasties is reduced in patients given gabapentin enacarbil.

Secondary Aim 4: To evaluate whether gabapentin enacarbil will improve patient's satisfaction.
Hypothesis: Patients are more satisfied with the pain and quality of life after taking gabapentin enacarbil compared to placebo, as assessed using the quality of recovery score (QoR-15).

3. STUDY DESIGN

3.1 General Design

A randomized controlled trial to determine the effect of gabapentin enacarbil on opioid consumption and pain scores in patients having primary hip or knee replacement surgery with spinal anesthesia. Randomization will be web-based and stratified by type of surgery. Allocation will be concealed until shortly before drug/placebo administration.

Participating patients will be randomly assigned to standard management with GEn or to standard management with placebo. Patients will be given GEn 600 mg bid or placebo 600 mg bid for 1 preoperative day and will receive 600 mg GEn or placebo about 2 hours before surgery and then restarted on GEn or placebo 600 mg within 6 hours of surgery, and then 600 mg bid for three additional days.

3.2 Primary Study Endpoints

To assess whether gabapentin enacarbil improves quality of postoperative analgesia characterized by decreased pain and/or opioid requirements after hip or knee surgery. Cumulative opioid consumption in the PACU and floor for the first 72 hours after surgery or till discharge whichever comes first. The total dose of opioid administered includes the background analgesia provided by morphine PCA, fentanyl PCA or hydromorphone PCA, rescue doses of IV fentanyl, IV

hydromorphone, and PO oxycodone. All opioids will be converted into morphine equivalents to standardize opioid consumption (10 mg of IV morphine = 100 mcg of IV fentanyl = 1.5 mg of IV hydromorphone = 20 mg of PO oxycodone the total number of requested PCA boluses will also be recorded, along with the number of requests that were actually delivered.
Postoperative pain intensity will be evaluated in the PACU using a 0-10 Numeric Rating Scale (NRS), where 0 is no pain and 10 is the worst possible pain. Pain will be assessed every 15 min for the first one hour after surgery and then every morning for three post-operative days as long as the patients are hospitalized.

3.3 Secondary Study Endpoints

1. To assess whether gabapentin enacarbil decreases the incidence of persistent incisional pain three months after surgery when used as a modality of pre-emptive analgesia. Patients will be invited to respond at 90 days to questions that are suitable for a telephone interview: any development of new pain or persistence of pain over the surgery site. After 3-months patients will be asked if they experience incisional area pain.

2. To evaluate whether gabapentin enacarbil decreases nausea and vomiting during the initial 72 hours after knee or hip surgery. The incidence of opioid related adverse events e.g. Post-operative nausea and vomiting during the first 72 hours after surgery.

3. To evaluate whether gabapentin enacarbil will decrease length of stay in the hospital. Duration of hospital length of stay in days will be calculated.

4. To evaluate whether gabapentin enacarbil will improve patient's satisfaction. Patient satisfaction will be performed by Outcomes Research Department personnel by using the QoR-15 satisfaction score.

4. SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

To be eligible for entry into this study, candidates must meet all of the following eligibility criteria at the time of randomization:

1. Men or women 18-85 years of age.
2. Scheduled for elective knee or hip arthroplasty with spinal anesthesia.

4.2 Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of randomization.

1. Creatinine >1.50 mg/dl.
2. History of clinically important current depression or currently on any prescribed anti-depressant medication.
3. Previously enrolled in any Xenoport trial.
4. Use of gabapentin or gabapentinoids (Lyrica, Horizant, Neurontin or Gralise) within one month.
5. Allergy to gabapentin or gabapentinoids (Lyrica, Horizant, Neurontin or Gralise).
6. Women who are pregnant or breastfeeding.

7. History of seizure disorder within the last one-year or taking medications for seizures.

4.3 Subject Recruitment and Screening

Screening visit would be within a month before surgery at the pre-operative clinical evaluation visit. Patients will be screened using inclusion and exclusion criteria. The study will be explained to the patients in detail. Participating centers are required to document all screened candidates initially considered for inclusion in this study and to specifically state the reason(s) for their exclusion. A screening log will be maintained in REDCap, which is a Cleveland Clinic internal database system. All screened candidates will be documented for inclusion and also reasons for exclusions from the study.

4.4 Early Withdrawal of Subjects

Patients will be free to withdraw from study at any time. Subjects must be withdrawn from the study for the following reasons:

1. Voluntary withdrawal
2. Adverse event or serious adverse event deemed necessary by investigator for patient safety.
3. Unable to take medication for three post-operative days

4.5 Data Collection and Follow Up for Withdrawn Subjects

1. Data obtained from electronic medical records will include: operation time, surgery type, intraoperative opioid consumption, postoperative opioid consumption in PACU and in ward, breakthrough pain medication requirements, pain scores in PACU and ward, requirement of antiemetics for nausea and vomiting, requirement of antihistaminic medications, requirement of laxatives for constipation, ambulation time, flatus, ileus, bowel movements, length of stay and any side effects or complications.
2. Preoperative and postoperative laboratory data including but not limited to renal function results will also be collected from electronic medical records. Patient functionality will also be recorded including, bathing, toileting, walking and moving.
3. Patients will be evaluated for pain (using numerical rating scale) (NRS) once in the PACU (Post-Anesthesia Care unit) every 15 minutes during the initial first hour after surgery and then on the first, second and third post-operative morning. Amount of opioids used, rescue anti-emetics used, nausea, vomiting and pain scores will be documented in EPIC.
4. With all study patients, post-operative pain at rest will be collected and reflected using the Numerical rating scale (NRS) pain scale. The patient is asked to rate the pain within (0-10), with zero indicating no pain and 10 indicating the worst imaginable pain.
5. Pain will be evaluated both at rest and after exercise as per physiotherapy protocol. This would be a global assessment of pain since the last assessment.
6. Patient satisfaction with their pain treatment will be questioned after 72 hours or at discharge whichever comes first using 0-5 scales and we will also use QoR-15 score to formally evaluate quality of recovery. The QoR-15 score is a validated scoring system allows quantification of patient's early postoperative health status, which is also a

description of quality of recovery. The QoR-15 score will be performed on 72 hours post op or at discharge whichever comes first.

7. Patients will be contacted by telephone at 3 months after surgery and queried regarding presence of new pain since surgery and its interference with activities of daily living. Phone call is made with the purpose of checking for pain conversion from acute to chronic and to check for any adverse event.

5. STUDY DRUG (or Device, Biologic, Treatment)

5.1 Description

Gabapentin is an analog of gamma-aminobutyric acid. It is currently approved by the US Food and Drug Administration for treatment for post herpetic neuralgia and seizure disorders. It binds to alpha-2 delta subunit of presynaptic P/Q voltage gated calcium channels, which regulate the release of excitatory neurotransmitters from nociceptive receptors. We would like to test an extended-release formulation of gabapentin enacarbil, a prodrug of gabapentin. GEn provides more sustained dose proportional exposure to gabapentin (unlike gabapentin), which may lead to more predictable exposure with GEn and decreased dosing frequency relative to gabapentin. Due to the mechanism of action of GEn and its predictable bioavailability due to it absorption via the MCT-11 transporters, we would like to prefer GEn to gabapentin.

5.2 Treatment Regimen

Gabapentin enacarbil 600 mg or placebo will be administered orally one day pre-operatively 12 hours apart with meals and 600 mg gabapentin enacarbil or placebo dose 2 hours before the surgery with sips of water. Post–operative dose of 600 mg gabapentin enacarbil or placebo should be resumed within 6 hours of completion of procedure with sips of water. Patient will receive 600 mg gabapentin enacarbil or placebo doses three additional days postoperatively 12 hours apart with meals.

5.3 Method for Assigning Subjects to Treatment Regimen

Participating patients will be randomly assigned to gabapentin enacarbil or placebo. Randomization will be web-based through REDCap and stratified by type of surgery. Allocation will be concealed until shortly before drug/placebo administration. Randomization will be stratified by type of surgery (hip versus knee). Randomization codes will web based using random-sized blocks, and treatment assignment (gabapentin enacarbil or placebo) will be done using a password-protected website administered by the Department of Outcomes Research statistical team at Cleveland Clinic.

5.4 Preparation and Administration of Study Treatment

Xenoport will supply Cleveland Clinic Fairview hospital and Cleveland Clinic Main Campus pharmacy with gabapentin enacarbil and identically looking placebo. Gabapentin enacarbil

or placebo will be administered orally with meals a day before the surgery, with sips of water pre-operatively and again with meals post-operatively. Both gabapentin enacarbil and placebo will have an identical package, with regards to appearance and physical properties. They will both be administered as oral tablets with sips of water or meals.

5.5 Subject Compliance Monitoring

Compliance with study drug will be monitored and recorded by study personnel based on information from the treating principal investigator and subjects. Subjects must be withdrawn from the study if they do not comply with the study drug regimen.

5.6 Prior and Concomitant Therapy

Patient will not receive any gabapentinoids from the start of study drug to the end of postoperative 72 hours period. All other pain medications will be allowed.

5.7 Packaging

HORIZANT ER 600mg tablets will be overencapsulated by the CCF IDS pharmacy. A matching placebo capsule will be compounded by the pharmacy to match that of the active study drug. Both will be packaged in vials containing ten capsules each, and will be dispensed accordingly to RedCap randomization (10 tablets per bottle).

5.8 Blinding of Study Drug

Principal Investigator and research fellow primarily involved in the study and follow-ups will be blinded to the treatment assignment. The study personnel listed above will not know or discuss the treatment assignment, medical history or status of any subject. Randomization will occur independently. Clinical evaluators for the outcomes will be blinded to group allocation and clinical research fellows not involved in evaluations will prepare the study drug/packet. Clinicians including nurses will be blinded to monitoring and will be required to perform their standard of care management after surgery**.**

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Cleveland Clinic Fairview hospital and Cleveland Clinic Main Campus will maintain accurate records of the receipt of the drug and will inform the sponsor and the principal investigator after the drug is received. Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files. The

investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.9.2 Storage

The study drug will be stored by the pharmacy on the shelf at room temperature. No special handling requirements during storage.

5.9.3 Dispensing of Study Drug

Cleveland Clinic Fairview hospital and Cleveland Clinic Main Campus will maintain accurate records demonstrating dates and amount of study drug received, to whom they are dispensed (subject-by-subject accounting), and accounts of any study drug accidentally or deliberately destroyed.

Study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the reconciliation form, and signed and dated by the study team.

5.9.4 Return or Destruction of Study Drug

The investigator will return all unused vials of study drug to Xenoport Inc. pursuant to instructions (unless agreed otherwise by Xenoport Inc.). At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Return or destruction of study drug will be done per Cleveland Clinic Fairview and Cleveland Clinic Main Campus pharmacy protocol.

6. STUDY PROCEDURES

6.1 Pre-registration and Screening

Medical history involves a detailed history of present illness. Any significant past medical or surgical history will be noted. Patient will be asked for any allergies to gabapentin or gabapentinoids (Neurontin, Lyrica, Gralise or Horizant).

Pre-op evaluation will be checking laboratory values through EPIC (electronic privacy information center). Available preoperative laboratory tests and medication list will be recorded. Renal function tests will be not be ordered exclusively for study purposes. Only pre-ordered renal function tests by the primary doctor will be used to screen patients. Only patients within the approved creatinine range (≤1.50 mg/dl) will be enrolled.

6.2 Visit 1 (Day of Surgery)

Patients will be given GEn 600 mg single dose with sips of water 2 hours before surgery and then restarted within 6 hours of completion of surgery. GEn will be administered to the patient 600 mg bid for three post-operative days with meals.

Physical evaluations include monitoring vital signs, checking general well-being and pain evaluation both pre-operatively and post-operatively. Patients will be evaluated by orthopedic

surgeons pre-operatively and post-operatively as per their protocol. Physical therapy will evaluate the patients for pain, mobility and strength as per physical therapy protocol. Physical therapy and orthopedic surgeons will record and document their findings in EPIC.

Patients will be monitored throughout their stay in the hospital and will be asked to report any adverse event or any untoward event to the research fellow. Patients will be also be inquired for any side effects during the phone call made 3 months after surgery.

Patient discharged prior to 72 hours will be followed-up via phone call(s). Phone call followup will be performed once a day till 72 hours.

6.3 Visit 2 (Phone call).

Patients will be contacted by telephone at 3 months after surgery and queried regarding presence of new pain since surgery and its interference with activities of daily living. Phone call is made with the purpose of checking for pain conversion from acute to chronic and to check for any adverse event.

6.4 Study Calendar of Procedures

	Pre-operative clinical evaluation visit (Outpatient)		Treatment Phase (Inpatient)					Follow Up (Phone call)
	Baseline/ Enrollment 1-2 weeks before surgery	2 Days prior to Surgery	1 Day Prior to Surgery (-1)	Day of Surgery (Day 0)	POD 1	POD 2	POD 3	3 Months after surgery
Screening visit1	**X**							
Randomization/ Enrollment	**X**							
Medical History2 / Disease History Pre-op Evaluation3	**X**			**X**				
GEn PO dose4 /Placebo			**X**	**X**	**X**	**X**	**X**	
Vital Signs	**X**		**X**	**X**	**X**	**X**	**X**	
Physician Evaluation5	**X**			**X**	**X**	**X**	**X**	
Monitoring and recording adverse events6			**X**	**X**	**X**	**X**	**X**	**X**
Data acquisition7	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Phone call		**X8**				**X10**	**X10**	**X9**

Footnotes:

[1] Screening visit would be within a month before surgery at the pre-operative clinical evaluation visit. Patients will be screened using inclusion and exclusion criteria. The study will be explained to the patients in detail. The side effects of GEn will be explained and patients will be consented for the study during this time. After eligibility is confirmed, patients will receive complete information about the study both verbally and in writing. Informed consent will be obtained from the patients prior to randomization and study-specific procedures.

[2] Medical histories involve a detailed history of present illness. Any significant past medical or surgical history will be noted. Patient will be asked for any allergies to gabapentin or gabapentinoids (Neurontin, Lyrica, Gralise and Horizant).

[3] Pre-op evaluations will be checking laboratory values through EPIC (electronic privacy information center). Available preoperative laboratory tests and medication list will be recorded. Renal function tests will be not be ordered exclusively for study purposes. Only pre-ordered renal

function tests by the primary doctor will be used to screen patients. Only patients within the approved creatinine range (≤1.50 mg/dl) will be enrolled.

[4] Patients will be administered GEn 600 mg bid PO dose. Patient will be asked to take GEn 600 mg bid one day prior to surgery with meals. Patients will be given GEn 600 mg single dose with sips of water 2 hours before surgery and then restarted within 6 hours of completion of surgery. GEn will be administered to the patient 600 mg bid for three post-operative days with meals.

[5] Physical evaluations include monitoring vital signs, checking general wellbeing and pain evaluation both pre-operatively and post-operatively. Patients will be evaluated by orthopedic surgeons pre-operatively and post-operatively as per their protocol. Physical therapy will evaluate the patients for pain, mobility and strength as per physical therapy protocol. Physical therapy and orthopedic surgeons will record and document their findings in EPIC.

[6] Patients will be monitored throughout their stay in the hospital and will be asked to report any adverse event or any untoward event to the research fellow. Patients will be also be inquired for any side effects during the phone call made 3 months after surgery.

[7] Data will be collected through personal interview and through electronic medical records. Data will also be collected through the phone call made 3 months after surgery.

Pre-operative data collection:

1. Pain scores using numerical rating scores (NRS) during the pre-operative evaluation visit
2. Brief pain inventory (BPI) at pre-operative evaluation visit.
3. Demographic data to be obtained includes height (cm), weight (kg), age (yr.), gender, (ASA) physical status, and self-declared ethnicity.
4. Patients will be questioned for social history (tobacco) and medical history (pulmonary disease, kidney disease, diabetes mellitus, neurological disease, chronic pain conditions, illegal drug usage, alcohol abuse, myocardial infarction, previous surgery or stent placement and medications usage).
5. Available preoperative laboratory tests and medication list will be recorded.
6. Individual risk for nausea and vomiting will be determined using the Apfel score.

Post-operative data collection:

1. Pain scores using numerical rating scores (NRS):
   a. Every 15 minutes for the first hour after surgery.
   b. Every four hours after the first hour until 72 hours after the surgery.
2. Brief pain inventory (BPI) prior to hospital discharge or at 72 hours post op whichever comes first
3. The QoR-15 score to formally evaluate quality of recovery. The QoR-15 score is a validated scoring system allows quantification of patient's early postoperative health status, which is also a description of quality of recovery. The QoR-15 scoring will be done prior to hospital discharge or at 72 hours post op whichever comes first.
4. Data obtained from electronic medical records will include: operation time, surgery type, intraoperative opioid consumption, postoperative opioid consumption in PACU and in ward, breakthrough pain medication requirements, pain scores in PACU and ward, requirement of antiemetics for nausea and vomiting, requirement of antihistaminic medications, requirement of laxatives for constipation, ambulation time, flatus, ileus, bowel movements, length of stay and any side effects or complications. Preoperative and postoperative laboratory data including but not limited to renal function will also be collected from electronic medical records. Patient functionality will also be recorded including, bathing, toileting, walking and

moving.

[8] Phone calls will be made purely to remind patients to take their pre-operative medication.
[9] Phone calls will be made to check for any adverse event and with the intention to assess chronic pain.
[10] Phone call made for follow-up if the patient is discharge prior to 72 hours.

6.5 Laboratory Procedures

No samples (e.g., blood, tissue, etc.) need to be shipped offsite for analysis. We will not perform any procedures or tests.

7. STATISTICAL PLAN

7.1 Sample Size Determination

Sample size is fixed to be at 100 patients. We will recruit 100 patients having hip or knee arthroplasties with spinal anesthesia. 50 patients control will be given the placebo for five days and 50 patients will be given GEn 600 mg bid for five days.

Power consideration. Sample size is fixed to be at 100 patients. Power estimation is based on the analysis of superiority on opioid consumption because this analysis requires more patients than the superiority analysis on pain scores. As it is stated in the hypothesis to claim positive effect of gabapentin enacarbil at least on one of these outcomes should be superior. Assuming the pilot study recruited total 100 patients and coefficient of variation (SD/mean) of 0.7 for both groups, we would have about 90% power to detect the ratio of 0.63 in geometric means in opioid consumption (i.e., a geometric mean opioid consumption decreases more than 37% in gabapentin enacarbil patients) comparing gabapentin enacarbil patients to patients receiving placebo at significance level of 0.0125.

If the assumptions appear to be too optimistic and study turns out to be underpowered, nevertheless treatment effects and variability identified in this pilot investigation can be used to plan a future study with sufficient power.

7.2 Statistical Methods

The modified intention-to-treat approach will be utilized: patients who were randomized, had the procedure and received any amount of treatment will be included in the analysis. The per-protocol analysis (on patients who were randomized, had the procedure and followed the treatment regimen at least 50% of the times) will be conducted for the primary outcome as a sensitivity analysis.
First, randomized groups will be compared for balance on potentially confounding baseline demographic and preoperative variables using descriptive statistics.

Primary outcome. In the primary hypothesis, quality of postoperative analgesia will be characterized using both pain scores and total postoperative opioid consumption within 72 hours of the surgery or till discharge. We will consider gabapentin enacarbil group better than placebo group on the postoperative pain management if gabapentin enacarbil group is found noninferior (i.e., not worse) on both outcomes and superior on at least one of the outcomes. We define the a-priori noninferiority pain score delta as 1 point and the opioid delta as 1.1 for the ratio in geometric

means IV morphine equivalent doses (meaning 10% difference between group's median doses). Thus, our primary hypothesis will be assessed in a joint hypothesis-testing framework described by Mascha and Turan (42).

We will first estimate confidence intervals for the treatment effect for both pain score and opioid consumption. Assuming lognormal distribution of opioid consumption, we will evaluate the percent difference in geometric mean IV morphine equivalent dose between the two groups using a log-linear regression model. To evaluate the difference in mean pain scores we will first summarize the pain scores by computing time weighted average (TWA) pain score for each patient. Then we will use a linear regression model to assess the treatment effect on the TWA pain scores.

Our joint hypothesis testing will consist of two steps. First, we will evaluate the noninferiority of gabapentin enacarbil to placebo group on both outcomes. Noninferiority (being "not worse") of gabapentin enacarbil group will be concluded for both outcomes at the significance level of 0.025 if the upper limit of 95% confidence interval is below the corresponding noninferiority delta. Second, if noninferiority is concluded for both pain scores and opioid consumption, we will proceed to a 1-tailed superiority test on each outcome in the same direction as the noninferiority testing. Superiority testing will be done at the overall 0.025 significance level and will be adjusted for multiple testing (two outcomes) via Bonferroni correction (0.025/2=0.0125); superiority will thus be claimed for a particular outcome if the 97.5% confidence interval is below zero (below one for ration in geometric means for opioid). Overall Type I error rate for the joint hypothesis testing will be maintained at 0.025 (we choose 0.025 instead of 0.05 because we have to consider treatment effect both directions gabapentin enacarbil vs. placebo and placebo vs. gabapentin enacarbil) even though both noninferiority and superiority will be tested at the 0.025 level. This is because noninferiority on both outcomes and superiority on at least one is required to claim gabapentin enacarbil group better than placebo group, and thus the joint hypothesis framework is an intersection-union test (which does not require additional adjustment for testing two sets of hypotheses).

In addition to the confidence intervals, tests giving the P-values for noninferiority and superiority will be performed. For noninferiority, two 1-tailed t-tests for each outcomes will be done to assess whether the difference in means pain scores (or ratio in geometric means for opioid) is below the given delta (log of given delta for opioid). For superiority, two 1-tailed t-tests will be done in the same direction as the noninferiority testing to assess whether the difference in means pain scores (or ratio in geometric means for opioid) is below zero (one). Estimates of treatment effect and standard error will be based on the regression models described above. .

Secondary outcomes. We will compare two randomized groups on each secondary outcome using appropriate 2-tailed tests for superiority: t-tests or Wilcoxon rank sum tests for continuous outcomes as of duration of hospitalization and QoR-15 satisfaction score.
To assess if administration of gabapentin enacarbil decreases the incidence of nausea and vomiting within initial 72 hours of the surgery and the risk of pain conversion from acute to chronic chi-square tests will be used.

The significance level for the set of secondary outcomes will be preserved at 0.05 overall by using a criterion of $P < 0.05/4 = 0.0125$ for each test (applying a Bonferroni correction for multiple testing of the 4 secondary outcomes).

R statistical software version 2.12.1 (The R Foundation for Statistical Computing, Vienna, Austria)

and SAS statistical software version 9.3 (SAS Institute, Cary, NC, USA) for 64-bit Microsoft Windows will be used for all statistical analysis.

8. SAFETY AND ADVERSE EVENTS

8.1 Definitions

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event is any adverse event that is experienced by a subject who has received an investigational drug, but that does not necessarily have a causal relationship with the investigational drug.

8.2 Recording of Adverse Events

All adverse events (including pre-dosing and treatment-emergent) should be recorded in the subject's record (or, if applicable, in the adverse event section of the CRF) regardless of severity or relationship to investigational drug. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, and should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported within 24 hours.

8.3 Reporting of Serious Adverse Events

In accordance with 21 Code of Federal Regulations (CFR) Part 312.32 and the recommendations of the International Conference on Harmonisation (ICH) [Federal Register, October 7, 1997, Vol. 62, No. 194, pp. 52239-45], any of the following adverse events are to be classified as a serious adverse event (SAE):

- An event that results in death.
- An event that, in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event). This does not include an event that, had it occurred in a more severe form, might have caused death.
- An outcome that results in a congenital anomaly/birth defect diagnosed in a child of a subject who participated in this study.
- An event that requires or prolongs in-patient hospitalization.
- An event that results in persistent or significant disability/incapacity.
- Other medically important events that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an in-patient hospitalization.).

Any SAE required to be reported according to 21 Code of Federal Regulations (CFR) Part 312.32 and the recommendations of the International Conference on Harmonisation (ICH) [Federal Register, October 7, 1997, Vol. 62, No. 194, pp. 52239-45] that occurs regardless of whether or not the subject has undergone any study-related procedures or received investigational drug, through the completion of trial, will be reported to the FDA. The investigator will forward a copy of the report to Xenoport in the same time frame that it is submitted to the FDA.

The Investigator will notify the local IRB/IEC per local requirements.

.**Study Sponsor Notification by Investigator (if sponsor exists)**

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to: [Name of Sponsor, contact, phone, fax]

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.1 IRB Notification by Investigator

The Investigator will:

- Monitor and record all adverse events
- Determine the seriousness, causality, and severity of each adverse event
- Report all serious adverse events to the FDA according to the code of federal regulations
- Forward a copy of the report to Xenoport Inc. in the same time frame
- Actively and persistently pursue follow-up of serious adverse events
- Forward a copy of the follow-up information to Xenoport Inc.

"The following four types of events must be reported to the Ca IRB:

1. Adverse events that is serious, unexpected, and related or possibly related to participation in the research.
2. Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.

3. Other unexpected adverse events, regardless of severity, that may alter IRB analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.
4. Unanticipated Problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB.

8.3.2 FDA Notification by Sponsor (if applicable)

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.
If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Unblinding Procedures

Unblinding of the study drug may be deemed necessary to ensure patient's safety. This can be undertaken by the research personnel responsible for patient randomization. The PI should approve the request of unblinding whenever possible. This should be documented in the patient's source document, and the investigator must inform the sponsor of all subjects whose treatment was unblinded. In most cases, the unblinding is a part of managing a SAE, and will be reported with the SAE. In cases where unblinding was not associated with a SAE, unblinding should be reported in a timely manner (i.e. notification of the sponsor within 24 hours by phone or fax, followed by a written narrative of the event within 48 hours).

8.5 Stopping Rules

Subjects must be withdrawn from the study if there is any adverse event or serious adverse event deemed necessary by investigator for patient safety.

8.6 Medical Monitoring

During the course of the study, the Xenoport-designated Monitor will visit the Investigator(s) at regular intervals by prior arrangement. The monitoring visits will be conducted to ensure protocol adherence, appropriate subject enrollment, quality of data, and continued adequacy of the investigational site and its facilities.

8.6.1 Internal Data Safety Monitoring

The trial will be coordinated by an Executive Committee chaired by Prof. Daniel I. Sessler MD, with members including Prof. Alparslan Turan MD and Dr. Edward Mascha Ph.D. The Committee will review randomized data blinded to group (i.e., Group A/B) at intervals. They will consider enrollment, adverse events, and potential harms to patients.

9. DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality and Privacy

The subject will not be identified by name in any study reports, and these reports will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential.

9.2 Source Documents

Prior to any testing under this protocol, including screening tests and evaluations, all subjects will sign an informed consent form that complies with the requirements of both 21 CFR Part 50 and HIPAA before entering the study. Or, a consent form that complies with the requirements of 21 CFR Part 50 and a separate HIPAA compliant authorization form for the use of and disclosure of the subject's protected health information (PHI) will be obtained from the subject in accordance with local practice and regulations.

The background of the proposed study and the benefits and risks of the procedures and study will be explained to the subject. A copy of the informed consent document signed and dated by the subject will be given to the subject. Confirmation of a subject's informed consent will also be documented in the subject's medical records prior to any testing under this protocol, including screening tests and evaluations.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study (in hard copy or electronic format). All data requested on the CRF must be recorded, and all missing data must be explained. Include a copy of the CRFs as attachments to the protocol.

9.4 Records Retention

Appropriate, local, and/or institution-specific guidelines regarding retention of records must be followed.

10. STUDY MONITORING, AUDITING AND INSPECTING

10.1 Study Monitoring Plan

The PI will be responsible for implementing the study-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. The PI will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

10.2 Auditing and Inspecting

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform on-site audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested. The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and hospital compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data

collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institutional compliance and quality assurance offices.

11. ETHICAL CONSIDERATIONS

The sponsor and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study according to local regulations.

11.1 Declaration of Helsinki

The Investigator must follow the recommendations contained in the Declaration of Helsinki, amended at the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, with Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002. See Appendix II in Section 15.2.

11.2 Ethics Committee

The Investigator must obtain written EC/REB approval of the protocol, ICF, and other required study documents prior to starting the study. In addition, Xenoport must approve the investigational site's ICF submitted to the site's EC/REB.

11.3 Informed Consent

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment 4 for a copy of the Subject Informed Consent Form. This consent form will be submitted with the study protocol for review and approval by the IRB. The formal consent of a subject must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12. PUBLICATION PLAN

Xenoport Inc. reserves the right to a 30-day courtesy review of all publication materials, such as abstracts, posters, or manuscripts, related to the study prior to submission of such publication(s). Investigators should refer to their Clinical Trial Agreement for additional details regarding the disclosure of study results.

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