PennState

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Effectiveness of Sphenopalatine ganglion block for Post-Dural Puncture Headache; A pilot study

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NCT03430531

Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (http://irb.psu.edu). For all other research, do not delete the instructional boxes from the final version of the protocol.**
5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

Table of Contents

1.0 Objectives

1.1 Study Objectives

To study the effectiveness of Spheno-Palatine (SP) ganglion block to alleviate the pain of post-dural puncture headache (PDPH).

1.2 Primary Study Endpoints

1. To study the effectiveness of SP ganglion block in relieving post-dural puncture headache in terms of

a. Number of subjects who get relief of pain
b. The onset time to pain relief after application of block
c. The duration of pain relief
d. The incidence of recurrence of post-dural puncture headache

1.3 Secondary Study Endpoints

1. To monitor any complications due to SP ganglion block
2. To measure patient satisfaction
3. To monitor any residual effects at 1 months after the SP block

2.0 Background

2.1 Scientific Background and Gaps

Lumbar puncture is a commonly performed diagnostic procedure in medicine and also for anesthesia. Inadvertent dural puncture can occur during epidural anesthesia and placement of an epidural catheter. Headache after a dural puncture is not uncommon and is excruciatingly painful. Most often it is self-limited and the pain subsides within 1-2 weeks. However, if left untreated, it can lead to considerable morbidity including chronic neck and back pain, subdural hematoma, seizures and even death.

According to the Headache Classification Committee of the International Headache Society, headache after lumbar puncture is defined as “bilateral headaches that develop within 7 days after a lumbar puncture and disappears within 14 days. The headache worsens within 15 min of resuming the upright position, disappears or improves within 30 min of resuming the recumbent position”. This definition helps to avoid confusion with migraine or simple headache after lumbar puncture.

Currently, the standard practice to manage this headache is to do an epidural ‘blood-patch’, wherein an anesthesiologist performs an epidural puncture in the lumbar spine after numbing the skin and subcutaneous tissue with 2-3 ml of 2% lidocaine and injects 20-30ml of the patient’s blood into the epidural space. The intention is for the blood to clot and seal the dural puncture. This is effective about 90% of the time and can be repeated if it fails. Introduction of infection, arachnoiditis, or another inadvertent dural puncture are possible complications. Some patients opt not to have the epidural blood patch for fear of another inadvertent dural puncture and choose the conservative management.

The other forms of therapy are strict bed rest for up to 7 days, hydration, caffeine, and epidural saline infusion. There are case reports of managing PDPH with administration of ACTH.

There are a few case reports about use of SP ganglion block for PDPH but no prospective studies looking at onset, duration, side effects and long term follow up after Sphenopalatine ganglion block.

2.2 Previous Data

Here at HMC, we have performed the SP ganglion block in two patients who could not be offered epidural blood patch because they were on anti-coagulants. The block was effective and both were back to normal activities of daily living within 24h.

2.3 Study Rationale

According to the Monro-Kellie hypothesis, within the confines of the cranium, the volume of CSF, blood and brain matter is kept in harmony. Changes in volume of any one will cause compensatory changes in one or both of the other.
A dural puncture causes loss of CSF and this is compensated for by an increase in cerebral blood flow (CBF) by vasodilatation, which in turn causes headache. This vasodilatation is mediated by parasympathetic inputs that synapse in the Sphenopalatine ganglion. Blockade of this ganglion would reduce parasympathetic activity and mitigate the headache.
SP ganglion block has been used to treat migraine and cluster headaches.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Age greater than or equal to 18 years
2. Complains of symptoms suggestive of post-dural puncture headache
3. Has a history of dural puncture (lumbar puncture or accidental dural puncture during epidural placement) within the previous 7 days
4. Sex: male or female (including nursing females)
5. Fluent in written and spoken English

3.2 Exclusion Criteria

The following groups of patients will be excluded

1. Those with a known history of hypersensitivity to local anesthetics of the amide type or to other components of GLYDO
2. Those with any congenital or acquired, anatomical deformity of the nostril, which preclude performing the block
3. Pregnant woman
4. Tumors of the nasal cavity, sinuses, and nasopharynx
5. Hypertension
6. Hereditary hemorrhagic telangiectasia
7. Use of anticoagulants such as clopidogrel, or warfarin
8. Clotting factor (e.g. Von Willabrand's disease (most common), Factor VIII deficiency (Hemophilia A), Factor IX deficiency (Hemophilia B), and Factor XI deficiency)
9. History of epistaxis within the prior 30 days
10. Those who refuse to consent to participate in the study
11. Patients who have had a failed epidural blood patch
12. Cognitive Impairment
13. Prisoner

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

If a patient consents to participate but cannot tolerate the procedure of SP block, then they will be removed from the study

3.3.2 Follow-up for withdrawn subjects

If the subject is withdrawn from the study, they will be offered other forms of therapy and followed up, if they allow.

4.0 Recruitment Methods

4.1 Identification of subjects

Patients who develop PDPH, both in-patients and those who arrive in the Emergency Department (ED) are referred to the Anesthesiologists-on-call, for management. A system will be set in place to inform one of the investigators when such a patient is referred. If suitable, one of the investigators will consent the patient and perform the block.

4.2 Recruitment process

When informed, one of the investigators will approach the patient and explain the study and if they are willing will consent them and perform the block.

4.3 Recruitment materials

None.

4.4 Eligibility/screening of subjects

Not applicable

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

When identified as a potential candidate for the study in the ward or in the ED by one of the physician investigators. The consent will be reviewed with the patient by one of the physician investigators. The consent will be signed at that time if the subject is willing to participate in the research.

5.1.1.2 Coercion or Undue Influence during Consent

Patients that are enrolling in the study will be told that participation is voluntary and will not in any way compromise the standard of care that they will receive.

Physician investigators will explain that the current standard treatment is bed rest, hydration and analgesics or an epidural blood patch. They will be free to choose any of the options.

5.1.2 Waiver or alteration of the informed consent requirement

A waiver of consent is requested to review medical record information to determine preliminary eligibility to participate in the research.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

The consent process will be documented in writing with the long form of consent documentation:

- The current IRB approved consent form will be obtained.
- We will verify that we are using the most current IRB-approved version of the study specific consent form and that the consent form is in language understandable to the subject.
- A copy of the consent form will be provided to the subject.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Not applicable

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Not applicable

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Not applicable

5.3.2.2 Adults Unable To Consent

Not applicable

5.3.2.3 Assent of Adults Unable to Consent

Not applicable

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Not applicable

5.3.3.2 Assent of subjects who are not yet adults

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Not Applicable

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the Research Data Plan Form.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Study information will be destroyed after the research has ended and all institutional/regulatory requirements for data retention have been met

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Information must be obtained from the subject's electronic medical record during recruitment to determine eligibility and, in some cases, to confirm information discussed with the subject in regards to their medical history

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The waiver is requested only for recruitment to determine subject eligibility to ensure that no medical conditions that fall into the exclusion criteria are present and would thus preclude enrollment. This waiver will minimize the enrollment of subjects' who may ultimately fail to meet the study inclusion/exclusion criteria.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Open-labelled, single arm, pilot study

7.2 Study Procedures

7.2.1 Study Intervention:

A urine pregnancy test will be done for all non-post-partum women.
Once the patient consents to participate in the study the following will be done.

- The worst pain score (on a scale 0-10) that the patient experiences while sitting at the edge of the bed for 5 minutes, will be recorded.
- An IV catheter will be placed and an infusion of IV fluid will be started, if the patient does not have already.
- Continuous ECG, pulse-oximeter and non-invasive blood pressure monitoring will be established and a skin temperature will be recorded.
- The patient will be placed in the supine position with the neck slightly extended.

Sphenopalatine block

Anatomy: The Sphenopalatine or the Pterygopalatine ganglion is a small (5 mm), parasympathetic ganglion located in the pterygopalatine fossa, posterior to the middle nasal turbinate. It is separated by a thin layer of connective tissue and mucosa from the nasal cavity.

Lidocaine (2%) Swab Preparation:

Use of cotton-tipped plastic applicator with 2% Lidocaine jelly applied (see section 7.4.6.3): One 2% lidocaine treated cotton-tipped applicator will be gently inserted into each nostril, along the floor of the nose. Slight rotatory motion of the applicator will be used to insert it as far as it goes with the intention to reach the nasopharyngeal wall (posterior wall of the nose). At that position the applicator will be left undisturbed for 5 minutes. The swabs will be taken out and this will be repeated twice more, using fresh 2% lidocaine treated swabs. The whole procedure will take about 30 minutes.

After the procedure the patient will be asked for any side effects and if they are comfortable will be asked to sit up with their legs dangling over the side of the bed. If they can sit for about 15

minutes without pain and are hemodynamically stable, they will be asked to stand and walk. At any stage the headache returns or they cannot sit up or stand for any other reason, they will be made to lie down.

If the headache resolves, they will be discharged to go home, if acceptable by the primary physician. The patient will be encouraged to drink plenty of fluids and caffeinated drinks and get as much bed rest as possible for the next 3 days.
After the patient has given informed consent, 2% Lidocaine jelly (Glydo) obtained from pharmacy supply, just like any other standard of care medication and will be administrated and documented as any other standard of care medication. Post research intervention, a study team member will securely email Marisa Chew, Senior Representative Patient Accounts, at mchew@pennstatehealth.psu.edu within 24-48 hours with identifiers (MRN, FIN, and Date of Service). She will manually pull the charge from the patient's bill and direct the research charge to the Sponsor, in this case the Department of Anesthesiology and Perioperative Medicine.

On Day 1, 2, and 7 after the procedure, one of the investigators will call them to ask a set of questions about the headache and any side effects. A follow up phone call, at 1 month after the SP ganglion block, will be made to ask for any residual headache or other symptoms and their satisfaction with the management. (Data Sheet)

If the headache does not get relieved, the patient will have the option to undergo an epidural blood patch or opt for a conservative management of bed rest, analgesics and oral fluids. These options will also be available if the headache were to recur after the patient goes home.

We will also collect information (demographic details, past medical history, details of the procedure that led to the current headache) from the patient's medical record for this research.

7.2.2 Post-treatment Days 1, 2, 7

Patients will be followed up by either a visit, if the patient is an in-patient, or by phone if the patient is at home.
Questionnaire – pain relief, residual pain (intensity and location), side effects, nasal bleeding (See Data Sheet in supporting materials)

7.2.3 1 month Post-treatment

A follow up phone call at 1 month after the SP block will be made to ask for any residual headache or other symptoms and their satisfaction with the management.

7.3 Duration of Participation

The patients will be contacted on post –procedure Day 1, 2 and 7. During the phone call, they would be asked about their original complaints (headache, neck spasm), and if they have any new symptoms or discomforts.
The participants will be contacted by phone about 1 month after the procedure to ask if they have any residual neck or back pain or any other side effect. They will also be asked if they are satisfied with their management of PDPH
The follow-up phone calls will be made even if the SPG block fails and the subject opts for either an epidural blood patch or conservative management.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

2% Lidocaine jelly (Glydo) is an approved local anesthetic agent permitted to be used over mucosal surfaces.

7.4.2 Treatment Regimen

A maximum of 6 mL of 2% lidocaine will be used which is within the therapeutic dose.

7.4.3 Method for Assigning Subject to Treatment Groups

It is an open label single arm study.

7.4.4 Subject Compliance Monitoring

The patient needs to comply with the telephonic conversation

7.4.5 Blinding of the Test Article

Not a blinded study

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The 2% lidocaine jelly is dispensed as a single dose unit (syringe prefilled with 6 mL of medication) and be obtained by and stored in the inpatient Pharmacy according to their standard procedures.

7.4.6.2 Storage

The 2% lidocaine jelly will be obtained by and stored in the inpatient Pharmacy according to their standard procedures

7.4.6.3 Preparation and Dispensing

The 2% lidocaine jelly is dispensed as a single dose unit (syringe prefilled with 6 mL of medication) and will be obtained from the inpatient Pharmacy according to their standard procedures. The investigator will squirt 1ml of this medication onto the cotton tipped plastic applicator immediately prior to use.

7.4.6.4 Return or Destruction of the Test Article

These are single dose dispensers and unused drug will be discarded as per hospital policy

7.4.6.5 Prior and Concomitant Therapy

Not applicable

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Thirty

8.2 Sample size determination

Convenience Sample: This is a pilot study and this number was selected to complete this study over one year. The data collected will be used for a formal sample size calculation, if appropriate, to plan a larger study.

8.3 Statistical methods

It would be mainly descriptive statistics looking at time to onset of pain relief, the duration of pain relief, failure of the procedure to relieve PDPH, description and frequency of any side effects at one week and 1 month.
The number of patients who do not get any or inadequate pain relief and if they need an epidural blood patch, it will be considered a failure of this technique.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Review Form

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

Every patient will be reviewed for any harmful effects due to the SP ganglion block

10.2 Data that are reviewed

Refer to above

10.3 Method of collection of safety information

Safety information will collected by interview of subjects at the time of intervention. Afterwards, safety information will be collected by telephone interview.

10.4 Frequency of data collection

Data will be collected at the time of intervention, Day 1, 2 and 7 post-procedural days and 1 month following intervention.

10.5 Individuals reviewing the data

Principal investigator – Verghese Cherian M.D
Co-investigator – Kofi Owusu MD

10.6 Frequency of review of cumulative data

Data will be reviewed after every 5 patients have undergone intervention.

10.7 Statistical tests

It would be mainly descriptive statistics looking at time to onset of pain relief, the quantum of pain relief, the duration of pain relief, failure of the procedure to relieve PDPH, description and frequency of any side effects at one week and 1 month.

10.8 Suspension of research

Unexpected problems such as consistent trend of worsening morbidity in the immediate or long-term setting of study intervention

11.0 Risks

Insertion of the cotton swab stick into the nostril can cause:
- mild pressure or a feeling like you have to sneeze
- brief mild discomfort or irritation in the nose
- brief or quick burning sensation
- bad taste in your mouth as some of the lidocaine may drip down into your mouth
- tearing and a brief temperature change
- temporary numbness in the throat related to a small amount of the lidocaine dripping into your mouth (This numbness should not last more than a few hours. During this time, it is safest if you avoid eating or drinking anything to avoid the risk of choking)
- nasal bleeding or infection have been reported, in some cases may be severe bleeding
- rarely, a temporary increase in pain has been reported

You may have temporary or no relief from procedure
There is a possibility of an allergic reaction to lidocaine.

Loss of confidentiality
Nursing mothers: The amount of lidocaine that may be absorbed into the blood stream, from this procedure, and excreted in the breast milk is minimal, and studies have shown that if nursing mothers undergoes even dental treatment with lidocaine, it is safe to continue breast-feeding.[6]
From the Glydo package insert:
Lidocaine is not contraindicated during labor and delivery. Lidocaine is secreted in human milk. Although, safety and effectiveness of lidocaine in pediatric patients have not been established, a study of 19 premature neonates where about 7mg/kg of lidocaine was used to lubricate intranasal tubes, the plasma levels of lidocaine was acceptable.
However, if our subject is breast-feeding then we will advise her NOT to feed her baby for next 4h and to express the breast milk and discard.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects
The SP ganglion block may reduce the PDPH

12.2 Potential Benefits to Others
If found effective, this could provide a less invasive alternative management for PDPH

13.0 Sharing Results with Subjects

Not applicable

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not applicable

15.0 Economic Burden to Subjects

15.1 Costs

The research will pay for the costs of the medication used for the SP ganglion block (Lidocaine 2%) and its administration.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Penn State Health Milton S. Hershey Medical Center, Hershey PA

16.2 Feasibility of recruiting the required number of subjects

Over a 1-year period, the study would have access to approximately 50 potential subjects.

16.3 PI Time devoted to conducting the research

The PI is allotted academic time for research and other scholarly activities

16.4 Availability of medical or psychological resources

All resources and facilities of HMC are available to subjects on study.

16.5 Process for informing Study Team

Each member of the study will complete CITI training. The procedure will be done by or under supervision of the PI. Additionally research team will meet monthly to review procedures and protocols.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

Not applicable

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related

Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility*. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.2 Recording of Adverse Events

Research subjects will be routinely questioned about adverse events during the procedure and in the follow-up phone calls.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms

- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

Not applicable

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

Not applicable

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

Not applicable

19.7 Stopping Rules

If the SP block is not effective in relieving the PDPH or is associated with morbidity due to the procedure, in the first 5 subjects, the study will be terminated.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

Not Applicable

20.1.2 Safety Monitoring

Not applicable

21.0 Future Undetermined Research: Data and Specimen Banking

Not applicable

22.0 References

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