Version Date: 3/17/2022

CONSENT FOR RESEARCH
Penn State College of Medicine
Penn State Health

Title of Project:	A Single Dose Pharmaco-Diagnostic for Peripheral Nerve Continuity After Trauma
Principal Investigator:	Kenneth Taylor, MD
Address:	500 University Dr., PO Box 850, EC089, Hershey, PA 17033
Telephone Numbers:	Weekdays: 8:00 a.m. to 5:00 p.m. (717) 531-4686. After hours call (717) 531-8521. Ask for the orthopaedic surgery doctor on 24-hour call.

Subject's Printed Name: _____

We are asking you to be in a research study.

Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you, and there will be no penalty or loss of benefits to which you are entitled.

This form gives you information about the research. Please ask questions about anything that is unclear to you and take your time to make your choice.

KEY INFORMATION

The following is a short summary of this study to help you decide whether or not to be a part of this research. More detailed information is provided later in this form. If you have any questions, be sure to ask the study team.

Why am I being invited to take part in this research study?

We are asking you to take part in this voluntary research study because you have a peripheral nerve injury (peripheral nerves control movement in your arm or leg).

What is the purpose of this research study?

The purpose of this voluntary research study is to investigate using a medication (4-aminopyridine (4-AP), also known as dalfampridine) as a possible test to see if the damaged nerve has been partially or completely cut.

How long will the research study last?

The study will last for 20 weeks.

What will I need to do?

If you chose to participate, you will be given one dose of either a drug called 4-AP or a fake drug (placebo) by mouth. You will then spend about 8 hours in an observation unit to monitor your function, and the level of the drug in your blood while having testing of your nerves and muscles to examine any

changes in function. After you go home from this visit, you will return to clinic for follow-ups at 2, 6, 12, 18, and 20 weeks after your dose of the medication. You will complete a phone interview at weeks 9 and 15. Standard of care visits are at weeks 2, 6, 12, and 18. Visits that are for this research study only are at weeks 9, 15, and 20.

Randomization: Whether you receive drug or placebo is totally random. This is so that we can compare the effects in some study subjects with the drug to study subjects who just had a fake pill. You will be unaware of which you received for the entire time of the trial.

What are the main risks of taking part in the study?
For this study, the main risks to know about are: potential loss of confidentiality, allergic reactions to the medication, kidney or bladder infection, seizure, and pain at the needle site used in one of the neuromuscular tests.

What are the possible benefits to me that may reasonably be expected from being in the research?
There are no benefits to you from taking part in this research. Results of the study may benefit other people in the future by helping us learn more about the use of this drug in nerve injury.

However, you may discover, through this trial, whether or not your nerve was severed or is intact. If you are given the real drug (4-AP) during randomization and you feel your limb again, then your benefit will be that the drug test worked to make you, and your doctors, know that your nerve is not fully cut. If you cannot feel or move your limb any differently during or after the trial, then you may not have a connected nerve, or it could be that you received placebo and no effect can be expected. Because we don't know which group (treatment or placebo) you are in, and we don't know if your nerve is severed or not, we cannot guarantee benefits to you from taking part in this research. However, please note that the return of function/ability to feel the limb is expected to only last during the testing period.

What happens if I do not want to be in this research?
Participation in research is completely voluntary. You can decide to participate or not to participate and this will not affect your treatment.

You may choose not to take part in this research study.

DETAILED INFORMATION
The following is more detailed information about this study in addition to the information listed above.

1. Why is this research study being done?

You are being asked to take part in this voluntary research study because you have a peripheral nerve injury (peripheral nerves control movement in your arm or leg). Peripheral nerves also allow to you to feel everything that touches your arm or leg. When peripheral nerves are injured people often cannot feel or cannot move parts of their limbs). Because your injury is so recent, there is no way to know for sure if the damaged nerve has been partially or completely cut. This is important information to help you and your doctor choose the best treatment. We are investigating using a medication named 4-AP as a possible test to see if the damaged nerve has been partially or completely cut.

4-AP is approved for the treatment of other neuromuscular diseases, but for diagnosis of peripheral nerve injuries, it is investigational as per the Food and Drug Administration (FDA).

Approximately 50 people will take part in this research study at Penn State Health.

2. What will happen in this research study?

If you decide to participate in this study, you will first sign this consent form after all your questions have been answered to your satisfaction and also after you have had all the time you need to make a decision.

Visit 1:
The first visit will be in completed as an inpatient at the bedside and/or the Clinical Research Center (CRC) in Hershey Medical Center on the fourth floor of the hospital. Visit 1 lasts about 8 hours. During this time, you will be under observation of the research team and/or CRC staff. You will have the following tests:

-You will be asked about your current medications, including prescriptions, over-the-counter-medications, vitamins and supplements.

- You will receive an intravenous line (IV) and a sample of your blood (approximately 1 teaspoon) will be taken as a baseline before you take the medicine by mouth (orally).

- You will also be asked to perform movements and report sensation during a neuromuscular exam by a member of the study team with required specialization on the study.

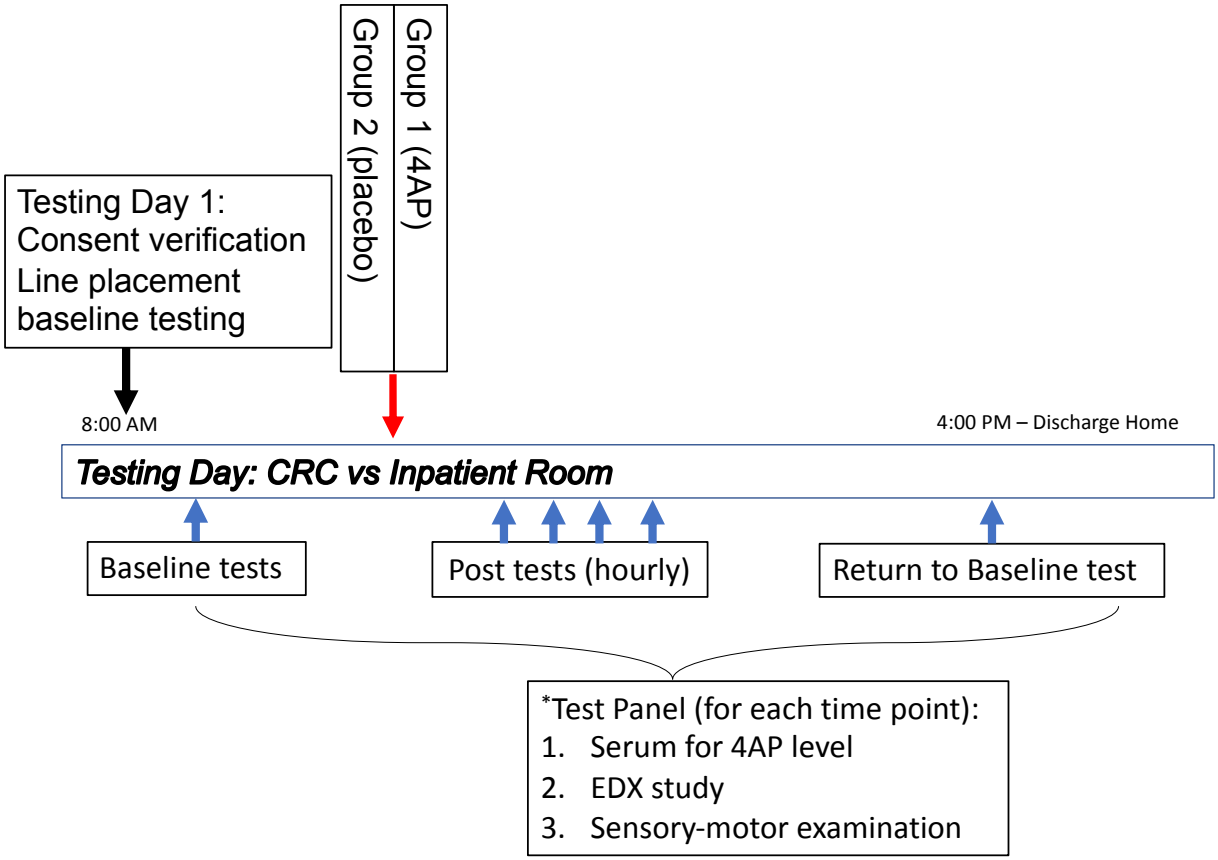
-This member of the study team with required specialization will also insert a needle near the peripheral nerve injury and perform an electrodiagnostic test (EDX testing) to record any electrical activity produced by skeletal muscles. The EDX test measures the electrical activity in your nerves and muscles. It consists of two parts: nerve conduction studies that measure the ability of specific nerves to transmit electrical impulses, or messages, to muscles and electromyography studies that measure the electrical activity of the muscles.

You will then be randomized (assigned by chance, like flipping a coin) to one of two groups. There is an equal chance that you will be assigned to either group. Neither you nor the research team will know which study group you are assigned to, but the research team will be able to get this information quickly if it is needed to ensure your safety.

Group A will receive an oral (a pill by mouth) dose of 10 mg of the investigational medication, 4-aminopyridine (4-AP).

Group B will receive an inactive substance called a placebo (in the form of a pill to be taken by mouth).

After the medication or placebo is taken, the neuromuscular exam, EDX testing and blood collection will be repeated hourly up to 5 times. The same testing will be done once again as a final “return to baseline” test and will be the 5th time. The total amount of blood taken at this visit will be about 6 teaspoons of blood.



In effect, we are testing if the drug helps return your nerve to function better than the placebo. The testing will continue during the whole time the investigational drug or placebo is in your system.

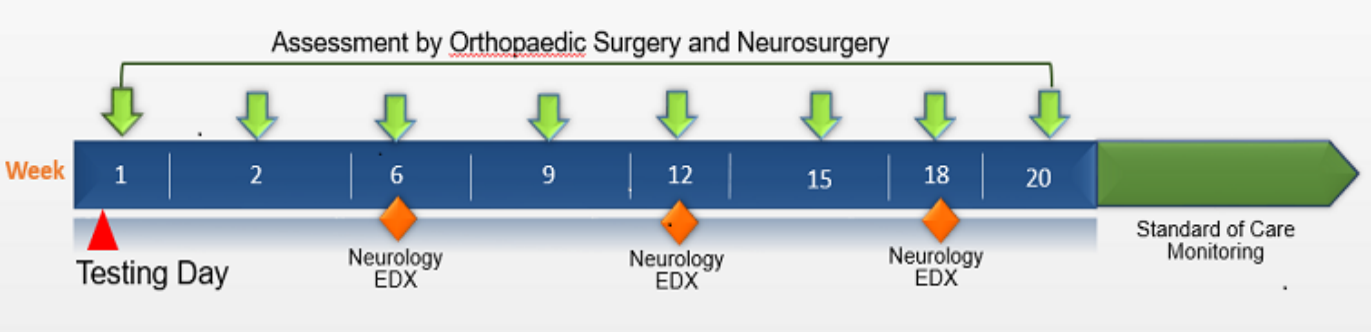
At the end of the testing period, you will be given a paper diary to record any symptoms such as movement, sensation, and pain that you experience over the next 20 weeks. The completed part of this diary will be collected by a member of the study team at the final follow up visit.

If you are being discharged to home following the completion of Visit 1, you will need to have a driver to take you home.

Follow-Up Visits:
Information from your standard of care follow-ups in clinic after this type of injury will be recorded. Your doctor in Orthopaedics or Neurology will perform a standard of care neurological exam at 2, 6, 12 and 18 weeks. You will undergo a standard of care EDX test at 6, 12, and 18 weeks after visit 1, and the information will be collected for the research study.

In addition to these standard of care follow ups, you will be contacted by a member of the study team via telephone at weeks 9 and 15 to ask you about any movement, sensation, and pain you are experiencing. A research visit for this study will be scheduled in the Clinical Research Center on the 4th floor of the main hospital at week 20. This visit include a physical exam by a trained study team member. The phone interview at 9 and 15 weeks and the follow-up visit at 20 weeks will last approximately 30 minutes.

You will be asked to bring your diary in for review at all follow-up visits. A member of the study team will collect your paper diary at the final week 20 visit.



You will be free to explore other treatment options during this follow-up period. Participation in this study will not limit other treatment options.

What are my responsibilities if I take part in this research?
If you take part in this research, your major responsibilities will include:

- Timely follow up at every appointment.
- For your safety, you must tell the study doctor or nurse about all the prescription drugs, herbal products, over-the-counter drugs (OTC), vitamins and other supplements you are taking. Check with the study doctor before starting any new medicines (including prescription, OTC drugs, vitamins and herbal supplements) or changing doses of medications that you are already taking.
- Report any changes in movement, sensation, pain, or other problems to your doctor.

3. What are the risks and possible discomforts from being in this research study?

Risks of 4-AP:
The study team will monitor you carefully for any side effects of the study drug. Side effects may include allergic reaction (shortness of breath, swelling of throat or tongue or hives), kidney or bladder infection or seizure. You could have a seizure even if you never had a seizure before.

Your chance of having a seizure is higher if you take too much study medication or if your kidneys have a mild decrease of function, which is common after age 50. Your kidneys will be checked before you start the study because healthy kidneys are needed to excrete or remove drugs from your system.

The study medication can also cause dizziness, confusion and balance problems. Therefore, you will be monitored on the only day that you will take the drug. During the study, if you are having problems or are experiencing any side-effects you should tell us as soon as possible.

If you experience significant side effects, including difficulty breathing, seizures, dizziness, confusion and/or balance problems please contact us immediately. Blinded data will also be evaluated periodically and the study will be terminated if a significant amount of side effects are encountered by patients in this trial.

Risk of randomization:
The primary risk of randomization is that the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments. You will be assigned to a treatment group by chance.

Risk of venipuncture:
The discomfort associated with removing blood by venipuncture (by needle from a vein) is a slight pinch or pin prick when the sterile needle enters the skin. The risks include mild discomfort and/or a black and blue mark at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure.

Risk of loss of confidentiality:
There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained as required by applicable law and to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

Risk of EDX testing:
EMG is a low-risk procedure, and complications are rare. There's a small risk of bleeding, infection and nerve injury where a needle electrode is inserted. Electrodiagnosic testing has the potential for mild discomfort from the placement of the electrodes through the skin into the muscle, as well as muscle tenderness or discomfort, which could last several days after completion of testing. Injuries are very rare but also include: bleeding, infection, and damage to nerves or soft tissues.

Other precautions

The person conducting the EMG will need to know if you have certain medical conditions. Tell the neurologist and other EMG lab personnel if you:

- Have a pacemaker or any other electrical medical device
- Take blood-thinning medications
- Have hemophilia, a blood-clotting disorder that causes prolonged bleeding

4. What are the possible benefits from being in this research study?

4a. What are the possible benefits to me?

There is no guarantee that you will benefit from this research. If you are assigned to the active study drug group, the possible benefits you may experience from this research study include potential for changes in nerve function to your injured extremity during the time that the drug is active in your system. Also, since there are additional research visits included at two week intervals in this trial,

recovery will be followed with greater accuracy over time. If you are assigned to the placebo group, you are not expected to benefit from this research.

You may discover, through this trial, whether or not your nerve was severed or is intact. If you are given the real drug (4-AP) during randomization and you feel your limb again, then your benefit will be that the drug test worked to make you, and your doctors, know that your nerve is not fully cut. If you cannot feel or move your hand any differently during or after the trial, then you may not have a connected nerve, or it could be that you received placebo and no effect can be expected. Because we don't know which group (treatment or placebo) you are in, and we don't know if your nerve is severed or not, we cannot guarantee benefits to you from taking part in this research.

4b. What are the possible benefits to others?
The results of this research may guide the future treatment of peripheral nerve injury. Results of the study may benefit other people in the future by helping us learn more about the use of this drug in nerve injury.

5. What other options are available instead of being in this research study?

You may choose not to be in this research study.

Before you decide if you want to be in this research, we will discuss the other choices that are available to you. We will tell you about the possible benefits and risks of these choices.

Because it is investigational, the therapy offered in this research is only available to you if you take part in the research study.

6. How long will I take part in this research study?

If you agree to take part, it will take you 20 weeks to complete this research study. Visit day 1 will last approximately 8 hours. You will be asked to follow-up 7 times over 20 weeks. The 2, 6, 12, and 18 week follow-up visit include follow up procedures and assessments that are standard of care for your injury. Follow-up visits and/or phone interviews 9, 15, and 20 weeks are not part of standard of care but are necessary for research purposes.

7. How will you protect my privacy and confidentiality if I decide to take part in this research study?
7a. What happens to the information collected for the research?

Efforts will be made to limit the use and sharing of your personal research information to people who have a need to review this information. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed, and there may be situations where disclosure is required by law.

In our research files at Penn State Health (PSH) and Penn State College of Medicine (PSU) we will include these identifiers: your name, phone number, address, date of birth, medical record number, and a code number.

- A list that matches your name with your code number will be kept in a locked file in Dr. John Elfar's office.

- Your research records will be labeled with your code number and will be kept in a safe area in Dr. John Elfar's research office.
- Your research samples will be labeled with a code number and your initials and will be stored in Dr. John Elfar's lab with limited access to only research personnel.
- A copy of this signed consent form will be included in your PSH medical record. This means that other PSH healthcare providers will know you are in this study.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

7b. What will happen to my research information and/or samples after the study is completed?

Your information or samples that are collected as part of this research will not be used or distributed for future research studies, even if all of your identifiers are removed.

7c. How will my identifiable health information be used?

In general, under federal law (including the Health Insurance Portability and Accountability Act – HIPAA or privacy laws) your health information is private. By signing this form, you are authorizing us to collect, use, and disclose your identifiable health information, sometimes referred to as "Protected Health Information" or "PHI" under HIPAA, for the purposes of this research study. We will use and disclose your information only as described in this form, in the PSH Privacy Notice, and as may be required or allowed under the applicable privacy laws.

The research team may use the following health information:

- Past, present, and future medical records, including identifiable information
- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

The following people/groups may see, use, and share your identifiable health information:

- PSH/PSU research staff involved in this study
- The PSH/PSU Institutional Review Board (IRB), a group of people who review the research study to protect subjects' rights and welfare
- The PSH/PSU Human Subjects Protection Office
- The PSH/PSU Research Quality Assurance Office
- Non-research staff within PSH/PSU who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- Federal and state agencies (such as the U.S. Food and Drug Administration, the Office for Human Research Protections, the Department of Health and Human Services, and other U.S. or foreign government bodies that oversee or review research)
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Organizations that provide independent accreditation and oversight of hospitals and research
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- The PSH/PSU pharmacy

- The sponsor(s) of this study, monitors and auditors, and other people or groups it hires to help perform this research
- A group that oversees the data (study information) and safety of this research

These groups may also review and/or copy your original PSH/PSU records while looking at the results of the research study. It is possible that some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information. We share your information only when we must, and we ask anyone who receives it from us to protect your privacy.

Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your identifiable health information and samples may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

We may remove identifying information from your protected health information. Once we do this, the remaining information will not be subject to the privacy laws. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Because research is an ongoing process, your permission for the use, storage and sharing of your health information will continue indefinitely.

Your privacy rights:

- You have the right to refuse to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you will not be able to take part in this research study.
- You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing using the address on the front of this form. Once permission is withdrawn, you cannot continue to take part in the study.
- If you withdraw your permission, we will stop collecting health information about you for this study; we may continue to use and share your health information that we already have if it is necessary for safety and scientific soundness of the research study; and we will not be able to take back information that has already been used or shared with others.
- You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. However, you may not be allowed to see or copy certain health information that is a part of this research study. This is only for the period of the study. You will be allowed to see that information when the entire research study is complete.

8. What are the costs of taking part in this research study?

8a. What will I have to pay for if I take part in this research study?

For costs of tests and procedures that are <u>only</u> being done for the research study:

- The 4-AP and placebo will be provided at no cost to you while you take part in this study.
- You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research and are outside the standard of care (what is normally done) for your condition.
- The research-related tests and procedures that will be provided at no cost to you include: All of the procedures completed during Visit day 1, follow-up visits at 9, 15,and 20 weeks.

For costs of medical services for care you would receive even if you were not in this research study:

- You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research.
- You and/or your insurance company will be billed for the costs of these routine tests and procedures in the usual manner.
- You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage.
- You will be responsible for any charges not reimbursed by your insurance company.
- Some insurance companies may not pay for routine costs for people taking part in research studies. Before deciding to be in this research you should check with your insurance company to find out what they will pay for.

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team.

8b. What happens if I am injured as a result of taking part in this research study?

It is possible that you could develop complications or injuries as a result of being in this research study. If you experience a side effect or injury and emergency medical treatment is required, seek treatment immediately at any medical facility. If you experience a side effect or injury and you believe that emergency treatment is not necessary, you should contact the principal investigator listed on the first page of this consent form as soon as possible and the principal investigator will arrange for medical treatment. You should also let any health care provider who treats you know that you are in a research study.

<u>PSH/PSU compensation for injury</u>

- There are no plans for PSH/PSU to provide financial compensation or free medical treatment for research-related injury.
- If an injury occurs, medical treatment is available at the usual charge.
- Costs will be charged to your insurance carrier or to you.
- Some insurance companies may not cover costs associated with research injuries.
- If these costs are not covered by your insurance, they will be your responsibility.

When you sign this form you are not giving up any legal right to seek compensation for injury.

9. Will I be paid to take part in this research study?

You will receive $80 for completion of Visit day 1. If you do not complete the study for any reason, you will be paid for the hours on Visit day 1 that you have completed based on $10 per hour. You will be provided with a $10 meal stipend for visit 1 completed at the CRC.

This reimbursement will be issued by an external company called Greenphire, which will issue your reimbursement. You will be issued a ClinCard, which is a debit card that your funds are loaded onto and can be used at your discretion. The research team will give Greenphire some personal information about you, as described below. Greenphire will only use your personal information to process this reimbursement and will not share it with anyone for any other purpose. Details of the debit card system are explained on an additional sheet. If you lose the card, you may be responsible for the replacement fee.

When a visit is completed, funds will be approved and loaded onto your card. The funds will be available within 2-3 business days. In order to assign a ClinCard to you and load funds onto the ClinCard, Greenphire will need your Study/Subject ID, Name, Address, date of birth and Social Security Number.

You will have the option to receive updates related to payment alerts via text message and/or email message. Standard text messaging rates will apply. In order to send you messages Greenphire will need your Mobile Phone Number and/or E-mail Address.

Payment received as compensation for participation in research is considered taxable income. If payments from Greenphire exceed $600 in any one calendar year, Greenphire will file a 1099 (Miscellaneous income) form on behalf of Penn State.

It is possible that your research information and/or specimens (both identifiable and de-identified) may be used to create products or to deliver services, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

10. Who is paying for this research study?

Funds from the Department of Orthopaedics will be used to support this research.

The institution and investigators are also receiving a grant from Cures Within Reach to support this research. Dr. John Elfar is an investigator on this study and has a patent on a separate 4-aminopyridine formulation other than the one being studied in this trial. Dr. Elfar also is an advisor to and holds financial interest in Peripheral Therapeutics, a company which studies 4-aminopyridine and nerve injury. This financial interest has been reviewed by the Penn State Institutional Review Board and Conflict of Interest Review Committee. If you would like more information, please contact the Conflict of Interest Program at 717-531-0003, ext. 283526.

11. What are my rights if I take part in this research study?

Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect medical information from your routine medical care. If you agree, this data will be handled the same as research data. If you withdraw completely from the research study, no further information will be collected and your participation will end. You may discontinue taking part at any time without penalty or loss of benefits to which you are otherwise entitled.

Your research doctor may take you out of the research study without your permission.

- Some possible reasons for this are: continuing the research would be harmful, your condition has become worse, you did not follow the instructions of the study doctor, you experience serious side effects.
- If your participation ends early, you may be asked to visit the research doctor for a final visit.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

12. If I have questions or concerns about this research study, whom should I call?

Please call the head of the research study (principal investigator), Dr. Kenneth Taylor at (717) 531-4686 or the orthopaedic surgery doctor on 24-hour call at (717) 531-8521 if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the research protection advocate in the PSH Human Subjects Protection Office (HSPO) at (717) 531-5687 if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns, complaints or general questions about the research.
- Have questions about your privacy and the use of your personal health information.
- You may also call this number if you cannot reach the research team or wish to offer input or to talk to someone else about any concerns related to the research.

You may visit the Penn State College of Medicine's Clinical Research web site at http://med.psu.edu/clinical-research/faqs for:

- Information about your rights when you are in a research study;
- Information about the Institutional Review Board (IRB), a group of people who review the research to protect your rights; and
- Links to the federal regulations and information about the protection of people who are in research studies. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (717) 531-5687.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

INFORMED CONSENT AND AUTHORIZATION TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative, provided the subject or subject representative an opportunity to discuss and consider whether or not to participate in the research, and have answered any questions about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent and Authorization

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject

By signing this consent form, you indicate that you voluntarily choose to be in this research and authorize your information to be used and shared as described above.

_____	_____	_____	_____
Signature of Subject	Date	Time	Printed Name