Wake Forest™
School of Medicine

Department/Section of Anesthesiology

# EFFICACY OF INTRATHECAL OXYTOCIN IN PATIENTS WITH NEUROPATHIC PAIN

Informed Consent Form to Participate in Research
James C. Eisenach, M.D., Principal Investigator

## INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have chronic nerve pain (burning or stinging type pain in the lower part of your body). Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

## WHY IS THIS STUDY BEING DONE?

This research study is being done because neuropathy or nerve pain is a significant problem for patients following surgery or traumatic injury. Currently available pain medications may not treat all types of pain or may treat pain only at doses that produce side effects and complications. The medication in this study may have a role in better treatment of pain. Oxytocin is commonly given by IV (into a vein) to treat certain types of pain. This is the third study in the United States to examine the effects of oxytocin given into the spinal fluid in the back. We believe that spinal oxytocin may prove to be an excellent pain killer for certain types of pain which sometimes occur with cancer or follow nerve injury after accidents or surgery. At present, there are not good treatments for this type of pain and your participation in this study may help researchers better understand this type of pain and perhaps develop new ways of treating this pain.

The goals of this study are to see if a dose of oxytocin, given into the fluid in your back near the spine has any effect on your current nerve pain.

Oxytocin has been approved by the US Food and Drug Administration (FDA), but the preparation and route of administration being used in this study has not been approved. At this time, there is not a form of Oxytocin that is available on the open market for spinal administration.

In this study oxytocin will be compared to placebo. A placebo is a substance, like a sugar pill, that is not thought to have any effect on diseases or medical conditions. In this study you will either receive the active study medication, oxytocin or placebo which is not active. Placebos are used in research studies to see if the drug being studied really does have an effect

## How Many People Will Take Part in the Study?

We will enroll 40 people at Wake Forest Baptist Health to take part in this study. In order to identify the 40 subjects needed, we may need to screen as many as 44 because some people will not qualify to be included in the study.
To be considered for inclusion in this study, you must have been vaccinated against SARS-CoV-2 (COVID-19). We will request to see a copy of your verification record (vaccine card or North Carolina Health and Human Services printed form).

## What Is Involved in the Study?

You will have five visits (detailed below) to the Clinical Research Unit (CRU). If you take part in this study, all of the test and procedures performed will be solely for research purposes.

You will be randomized into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in one of the two study groups.

Group 1- will receive 100 micrograms of spinal oxytocin in your first spinal injection and placebo (saline) in your second spinal injection
Group 2- will receive placebo (saline) in your first spinal injection and 100 micrograms of spinal oxytocin in your second spinal injection

Neither you nor the investigator will know which group you are in. This is done so that a fair evaluation of results can be made. This information is available to the researchers if needed in an emergency.

If you take part in this study, you will have the following tests and procedures:

**PROCEDURES**

**Vital Signs:** we will monitor your blood pressure, heart rate and oxygen saturation (amount of oxygen in your blood).

**Electrocardiogram (ECG):** tracing of the rhythm of your heart.

**Laboratory Testing:** female participants of child-bearing potential will have blood drawn to determine that they are not pregnant. Blood will be sampled 4 times after the spinal injection from the existing intravenous catheter.

**Thermal Heat Testing:** we will train you to accurately describe pain from a small heat

probe (1.5 inches). The tip of the heat probe that will be applied to you're the skin on your forearm is about the size of a penny. The thermal heat probe will be controlled by a computer that is programmed to deliver temperatures that range from skin temperature up to a temperature that is hot (124 ºF) and uncomfortable, but does not burn your skin. We will ask you to rate the pain by using a sliding scale. Most volunteers find that they can learn to tell very small differences in the temperature probe accurately.

**Light Touch Testing:** a von Frey filament (a plastic thread like a paint brush bristle) and a cotton wisp (Q-tip) will be lightly applied to your skin. We will ask you to tell us when you feel a difference in the sensitivity on your skin. We will use a washable marker to "mark" the areas that you tell us are more sensitive.

**Study Visit 1:**
During the first study visit we will explain all study related procedures, measure your blood pressure, heart rate, and we will place a clip on your finger which will measure the oxygen in your blood. We will perform an electrocardiogram (ECG), to obtain a baseline tracing of your heart and female participants of child-bearing potential will have approximately 1 teaspoon of blood drawn for a pregnancy test. We will also train you to rate pain in response to heat applied to an arm/leg that you are currently experiencing no pain (Thermal heat testing). We will use the von Frey filament (a plastic thread like a paint brush bristle) and a cotton wisp (Q-tip) to test your area of sensitivity in your area of nerve pain (Light touch testing). This visit will last approximately 2 hours.

**Study Visit 2:**
On the morning of the second session you will come to the Clinical Research Center (CRU) having had nothing to eat or drink after midnight. We will record your blood pressure, heart rate, the amount of oxygen in your blood, and we will connect you to a heart monitor. We will use the von Frey filament (a plastic thread like a paint brush bristle) and a cotton wisp (Q-tip) to test your area of sensitivity in your area of nerve pain (Light touch testing) and ask you to rate your pain using a plastic sliding scale. Then we will insert an intravenous catheter (IV) into a vein in your arm and you will get IV fluid through this catheter. We will also take 4 blood samples from this IV after your spinal injection of the study medication to check the level of oxytocin in your blood. If we cannot draw the blood from the IV catheter we will not perform a separate needle stick. You will have approximately 1 teaspoon of blood withdrawn from a vein 4 times throughout study visit 2.

We will then ask you to curl up into a ball on your side on a bed and put a spinal needle into the spinal space in the lowest part of your back after numbing the skin with lidocaine. After successfully placing the spinal needle, we will take a sample approximately one-half of a teaspoon of your spinal fluid and then we will inject the oxytocin or placebo according to the group that you were randomly assigned.

The spinal needle will then be withdrawn and you will be asked to lie on your back with the head

of the bed elevated slightly.

Multiple times during this day (from just before the spinal until 4 hours after the spinal injection) we will measure your blood pressure, measure the oxygen in your bloodstream with the finger-clip, examine you to test your arm and leg strength, and sensations, (to test for any changes in the strength or sensation you have in your arms and legs) and ask you to about any other sensations you may be experiencing. We will also monitor your electrocardiogram throughout the study period.

About 4 hours after the spinal injection we will stop gathering information for the study. To go home, you must not have any side effects that would prevent you from walking (like dizziness, unsteadiness). You must have someone drive you home and you must be available for us to call you at home. We will call you 6 hours after the spinal drug injection and 12 hours after the spinal drug injection. You must call us if you have any questions or concerns during this period. There is a remote chance that should you experience side effects which are concerning, we will keep you in the hospital overnight. This visit will last approximately 6 hours.

**Study Visit 3:**

You must return to the CRU approximately 24 hours after the spinal drug injection. You will have approximately 1 teaspoon of blood withdrawn from a vein during the 24 hour follow up visit to have your electrolytes evaluated. We will call you daily for 5 days, then weekly for 1 month, then approximately 6 months after the study and ask you about any symptoms that you believe you might have experienced and we will ask you to give us a verbal pain score. If at any time you have a question or a concern, please call us.

**Study Visit 4:**

At least one week after study visit 2 we will schedule you an appointment to return to the CRU for your fourth visit. On the morning of the fourth session you will come to the Clinical Research Center (CRU) having had nothing to eat or drink after midnight. We will record your blood pressure, heart rate, the amount of oxygen in your blood, and we will connect you to a heart monitor. We will use the von Frey filament (a plastic thread like a paint brush bristle) and a cotton wisp (Q-tip) to test your area of sensitivity in your area of nerve pain (Light touch testing) and ask you to rate your pain using a plastic sliding scale. Then we will insert an intravenous catheter into a vein in your arm and you will get IV fluid through this catheter. We will also take 4 blood samples from this IV after your spinal injection of the study medication to check the level of oxytocin in your blood. If we cannot draw the blood from the IV catheter we will not perform a separate needle stick. You will have approximately 1 teaspoon of blood withdrawn from a vein 4 times throughout study visit 4. The total amount of blood withdrawn during the entire study will be approximately 2 ounces.

We will then ask you to curl up into a ball on your side on a bed and put a spinal needle into the spinal space in the lowest part of your back after numbing the skin with lidocaine. After successfully placing the spinal needle, we will take a sample approximately one-half of a teaspoon of your spinal fluid and then we will then inject the oxytocin or placebo according to

the randomization that has been selected for you (this time you will receive opposite of what you received in your spinal injection on study visit 2). The spinal needle will then be withdrawn and you will be asked to lie on your back with the head of the bed elevated slightly.

Multiple times during this day (from just before the spinal until 4 hours after the spinal injection) we will measure your blood pressure, measure the oxygen in your bloodstream with the finger-clip, examine you to test your arm and leg strength, and sensations, (to test for any changes in the strength or sensation you have in your arms and legs) and ask you to about any other sensations you may be experiencing. We will also monitor your electrocardiogram throughout the study period.

About 4 hours after the spinal injection we will stop gathering information for the study. To go home, you must not have any side effects that would prevent you from walking (like dizziness, unsteadiness). You must have someone drive you home and you must be available for us to call you at home. We will call you 6 hours after the spinal drug injection and 12 hours after the spinal drug injection. You must call us if you have any questions or concerns during this period. There is a remote chance that should you experience side effects which are concerning, we will keep you in the hospital overnight. This visit will last approximately 6 hours.

**Study Visit 5:**

You must return to the CRU approximately 24 hours after the spinal drug injection. You will have approximately 1 teaspoon of blood withdrawn from a vein during the 24 hour follow up visit to have your electrolytes evaluated. We will call you daily for 5 days, then weekly for 1 month, then approximately 6 months after the study and ask you about any symptoms that you believe you might have experienced. We will also collect a verbal pain score during these follow ups. If at any time you have a question or a concern, please call us.

## Storage of Biological Tissue

If you agree to participate in this study, we will draw one-half of a teaspoon (2 milliliters) of cerebrospinal fluid (CSF) prior to injection of the study medication to use for future research. This sample will be kept and may be used in future research to learn more about other diseases. Your sample will be obtained in the Clinical Research Unit by the Anesthesiology Department at Wake Forest University Baptist Medical Center. The sample will be stored in the Pain Mechanisms Laboratory and it will be given only to researchers approved by Dr. James Eisenach. An Institutional Review Board (IRB) must also approve any future research study using your tissue sample. In order to participate in this study, you must be willing to provide this sample for future research.

Your CSF sample will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

The research that may be performed with your CSF sample is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your CSF will not be given to you or your doctor. The results will not be put in your medical record. The research using your CSF sample will not affect your care.

Your CSF sample will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

## How Long Will I Be in the Study?

You will be in the study for about 1-3 weeks. However we will contact you by telephone 6 hours and 12 hours after you leave the research clinic. We will also contact you daily for 5 days, weekly for a month and then at 6 months following your study.

You can stop participating at any time.

## What Are the Risks of the Study?

Being in this study involves some risk to you. The risks are given below. You should discuss the risk of being in this study with the study staff.

**Heat Probe**

You may experience brief pain during the thermal heat testing.

**Oxytocin**

The safety of spinal oxytocin has been extensively examined in animals, with no evidence of any nerve damage or other lasting effects, the FDA has approved this investigational study for humans, and nearly 1000 humans have received spinal oxytocin in China without reported problems. Although this all suggests that it is safe to administer oxytocin, the exact risks are unknown. We will monitor you for many theoretical problems such as your level of sleepiness, changes in your blood pressure, how fast your heart is beating, and your urge to breathe. We will treat any side effects that you may experience if the changes are enough to concern us.

**Spinal Procedures**

Risks associated with the spinal procedures are mild bruising and soreness in the area. There is a risk (less than 1%) of developing a headache from the spinal needles. If you develop a headache that does not go away and is bothersome, we will talk to you about an epidural blood patch. This is a simple procedure, which would involve putting a needle in the epidural space in your back and injecting some blood taken from your arm. This procedure is 95% (95 times out of 100) effective in treating the headache. However you would have a 1 in 3 chance of having a backache for a few days. Rarely (5 out of 100 times) is a 2nd blood patch needed. Other risks of the epidural blood patch are the same as the spinal. You will not be charged if you need an epidural blood patch to treat a headache. The risk of paralysis, infection or nerve damage from a

spinal procedure is extremely rare, less than one chance in 20,000. The numbing medicine that we put under your skin right before the spinal needle is inserted may cause you to have a brief period (about 5 seconds) of mild discomfort.

We may be unable to place the spinal needles due to the shape of your back. If we cannot place the spinal needles, you would no longer be able to continue participating in the study. You will be paid as detailed below.

**Risks from Needle Insertions**
You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions.

**For Electrocardiogram (ECG):**
The electrode pads used during the ECG may cause minor skin redness or irritation.

You can call the study staff at any time if you think you might be having any of the side effects discussed above. Also, the study staff will be telephoning you each day for 5 days after the study, then weekly for 1 month, then approximately 6 months after the study and ask you about any symptoms that you believe you might have experienced. If at any time you have a question or a concern, please call us.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study.

## Reproductive Risks and other Issues to Participating in Research

Pregnant women are excluded from participation in this study. Because some methods of birth control are not 100% reliable, a pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

## ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You may or may not benefit from participating in this study. We hope the information learned from this study will benefit other people in the future.

## WHAT OTHER CHOICES ARE THERE?

This is not a treatment study. Your alternative is to not participate in this study.

## WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** medical history and medication history.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Only the following people or organizations will be granted access to your Protected Health Information:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research

2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state law.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire and [Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished

You can tell Dr. James C. Eisenach that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

James C. Eisenach, M.D.
[redacted]

[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

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

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

## WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

## WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and/or effectiveness of Oxytocin administered spinally; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by National Institutes of Health which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

## WILL YOU BE PAID FOR PARTICIPATING?

You will be paid $800 (outlined below) if you complete all the scheduled study visits. If you withdraw for any reason from the study before completion you will be paid for the portion of the study that you completed.

- Placement of IV: $25 each (total of $50)
- Placement of Spinal: $100 (total $200) and study drug administration (if spinal placement is unsuccessful, the study will be abandoned and the subject paid for the portion completed)
- Completion of study visit 2 (first spinal injection): $150
- Completion of study visit 4 (second spinal injection): $250
- Completion of entire study: $150
- To receive the entire $800 you must complete all study related visits and procedures.

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

## WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the National Institutes of Health. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

## WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. James Eisenach at [redacted] or after hours you should call the study coordinator by calling [redacted].

## WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because you failed to follow instructions or because the entire study has been stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

## WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. James Eisenach at [redacted] or after hours you should call the study coordinator by calling [redacted].

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted].

You will be given a copy of this signed consent form.

## SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm