Basic Assessment of Safety and Minimally invAsive sTimulation via Injectrode (BASMATI)

Title: ***BASMATI*** **- Basic Assessment of Safety and Minimally invAsive sTimulation via Injectrode.**

Protocol number: NCP-01

Device: Neuronoff Basmati Injectrode

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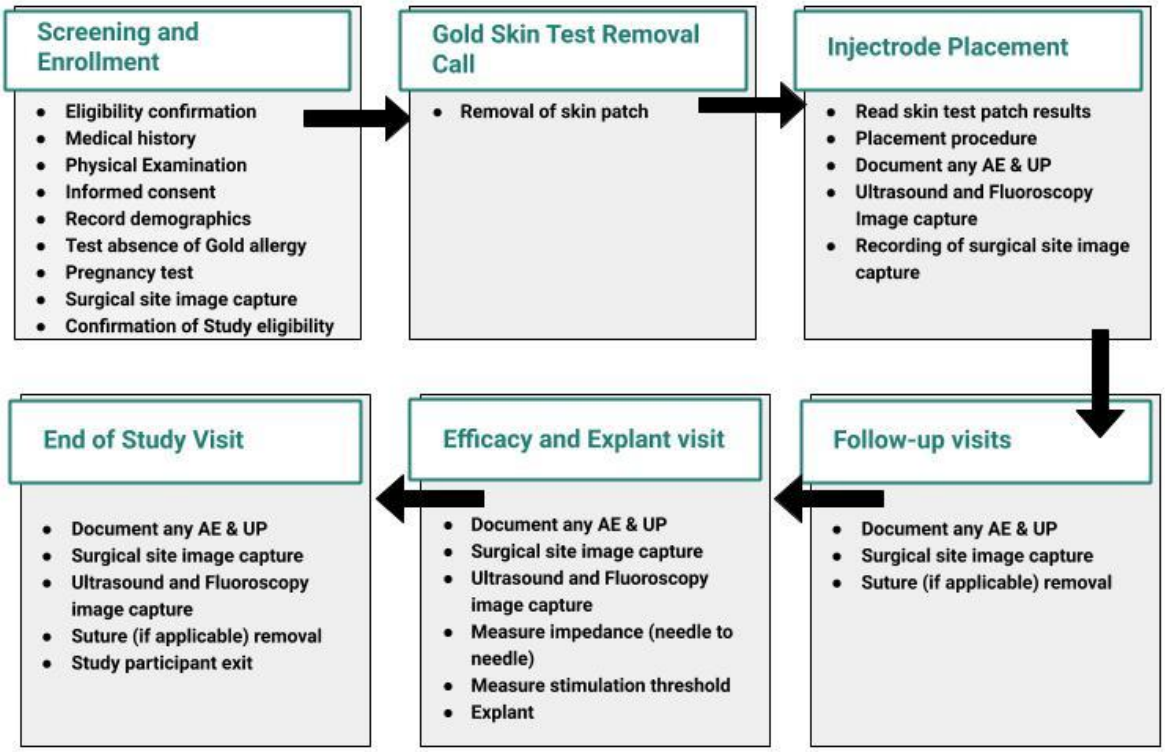
Revision	Revision Date	Sections Revised	Description	Person Issuing Change	DCO#
A	20201012	All	Initial Release	Shaher Ahmad	0041

Protocol Synopsis

Sponsor Contact Information	Neuronoff, Inc. 11000 Cedar Rd, Ste 290 Cleveland, OH 44146
Title of Trial	BASMATI - Basic Assessment of Safety and Minimally invAsive sTimulation via Injectrode.
Objective	The objectives of this non-significant risk (NSR) study are to evaluate the safety of the short term placement of the Basmati Injectrode for up to 28 days and the efficacy of conducting electrical current to stimulate subcutaneous nerves on the explant date just prior to explant.
Clinical Hypothesis	The 28 day temporary placement of a Basmati Injectrode does not result in unexpected levels of inflammation or encapsulation.
Investigational Device	A proprietary bio-electronic medical device (Neuronoff Basmati Injectrode Insert) which is capable of transmitting small electrical currents to stimulate sensory nerves.
Study Device description	The Basmati Injectrode is a gold wire coil formed into the shape of a grain of rice of 10mm length by 4mm width by 2 mm height. This gold material is of 99.99% purity and used in predicate medical devices as lead or electrode material in neuromodulation applications.
Comparative Data	Histopathological report describing findings in rodents with sub-chronic and chronic placement of the Injectrode (REC-020).
Study Design and Scope	The proposed study is a prospective, single-center, single-arm, non-randomized design. Up to 10 study subjects will be provided with the placement of an Injectrode insert. The maximal placement duration will be 28 days. Subjects selected to participate in the trial are healthy without any preexisting condition indicated to be treated. Each subject will be followed during the trial period of approximately 50 days, including the time for screening and post-explant follow-up. The study will end when the last subject has completed the trial period and exited. After exit from the clinical study, subjects will continue to be followed by their physician per standard of care. All device and procedure-related adverse events (AEs) and unanticipated problems (UPs) will be collected and reported per the study protocol.
Planned Enrollment	We plan to enroll and screen up to 20 study participants, of which up to 10 participants will be provided with a Basmati Injectrode Insert for the trial.
Primary Safety Objective	Primary measures of device safety will include verification of the absence of unexpected inflammation and minimization of excessive encapsulation around the Injectrode as verified by cell staining and pathohistological analysis.
Secondary Effectiveness Objective	Secondary measures of device effectiveness will include impedance and stimulation threshold measurements for subcutaneous nervous tissue.

STUDY FLOWCHART



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List of Abbreviations and Definitions

Abbreviation/Term	Definition
ADE:	Adverse Device Event
AE:	Adverse Event
CE:	Conformité Européenne (European Conformity)
CIP:	Clinical Investigational Plan
CRF:	Case Report Form
CTA:	Clinical Trial Agreement
EC:	Ethics Committee
FDA:	United States Food and Drug Administration
GCP:	Good Clinical Practices
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
ID:	Identification
IRB:	Institutional Review Board
ISO:	International Organization for Standardization
kHz:	Kilohertz
NRS:	Numeric Rating Scale
PW:	Pulse Width
SADE:	Serious Adverse Device Event
SAE:	Serious Adverse Event
SCS:	Spinal Cord Stimulation
SOC:	Standard of Care
UADE:	Unanticipated Adverse Device Effect
USADE:	Unanticipated Serious Adverse Device Effect
UP:	Unanticipated Problem
µsec:	MicroSecond
µA:	Micro Ampere

1.0 INTRODUCTION

1.1 Background and rationale

Neuromodulation, sometimes referred to as Bioelectronic Medicine, is using electrical stimulation or blocking of neural activity to achieve beneficial effects in the human body. These effects can include the reduction of chronic pain, reducing the frequency of overactive bladder, epileptic events, up to a modulation of the metabolic activity of inner organs. In many cases, afferent and efferent nerves of interest for interfacing are located within 5 cm when measured from the surface of the skin. Unfortunately, extracorporeal means of modulating neural activity in these nerves cannot be achieved reliably by widely available technologies such as Transcutaneous Electrical Nerve Stimulation (TENS) as the electric field applied on the outside of the skin only penetrates a few millimeters into the body before current densities have dissipated enough to limit the ability to reliably activate or deactivate neural tissue.

In order to electrically interface with these nerves, the clinical standard today is to place an implantable pulse form generator (IPG) into the patient, followed by one or more electrodes connecting the IPG to the nerve of interest by means of an open cut-down procedure. This often requires general anesthesia, a surgeon to place the devices, and commonly results in significant scarring visible post surgery as well as a large burden on the payer in the healthcare system for the cost of the extensive procedure.

1.2 Current treatment approaches and shortcomings thereof

Today, individuals suffering from chronic intractable pain of the trunk and/or limbs are typically treated on a continuum with less invasive therapies prescribed first. Established, non-surgical treatment options include, but are not limited to, oral medications including opioid-based drugs, physical therapy, TENS, acupuncture, nerve blocks, radiofrequency ablation and other options based on clinical judgment. The surgical treatment options for these study participants include surgery of the spine, sympathectomy, intrathecal drug pumps, and spinal cord stimulation (SCS) systems[1].

Neuromodulation offers many treatment solutions to pathologies such as Parkinson's Disease, peripheral nerve pain, overactive bladder (OAB) and neuralgia among others. Current solutions are divided between invasive, minimally invasive and non-invasive treatments and each come with their own set of challenges and benefits. Invasive treatments generally require surgery under anesthesia to place signal generators, leads and electrodes, often resulting in visible scars and are the most expensive treatment option. Non-invasive treatments typically have the least efficacy, reliability problems, limited applicability to a few locations and no ability to block nerves. Only few invasive treatments exist and those generally require a bulky external signal generator, and often don't provide the option to place an electrode as a cuff around a nerve, a necessary requirement for optimal mechanical and electrical interfacing for the long term. For many potential applications that could be treated with

[1] American Chronic Pain Association Resource Guide to Chronic Pain Medication and Treatment, 2014 Edition.

neuromodulation technology, nerves of interest are located deeper than 5 mm when measured from the surface of the skin. This limitation of non-invasive TENS technology to nerves only very close to the skin is greatly holding back the development of novel treatments using neuromodulation.

There is a need for a technology that conducts an externally generated signal to a nerve of interest to locations from just beneath the skin to a target nerve at a depth of up to 5cm.

1.3 Clinical need for a "last mile connection" to connect to a nerve

The future of neuromodulation is expected to become more patient centric and will focus on various unserved needs patients have today. One of these needs is to be free from the need to undergo revision surgeries every 3 to 7 years to replace an exhausted battery by explanting an old neuromodulation device and reimplanting a new one in its place. In addition, a second need is to minimize the prevalence and size of scars caused by the surgery to place first an electrode on a nerve target and second the scar caused by the placement of the signal generator.

Neuronoff, Inc. set out to provide a solution to both of these needs by electrically connecting the nerve with an insert that can be delivered via needle puncture to minimize scarring[2]. The insert functions as an electrical conduit (coupler), transferring current applied to the skin (e.g. via TENS) via a very low impedance down to the nerve of interest (figure 1). In essence, this conduit provides the last mile connection for electrical signals from the skin to the target nerve.

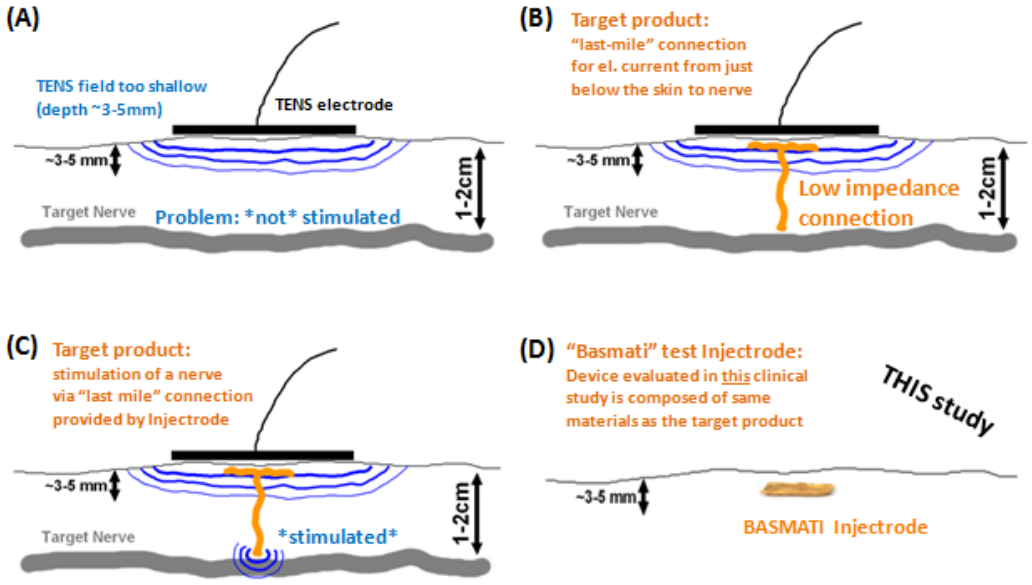

Figure 1: Comparison between the **Target Product (A-C)** and the **BASMATI Injectrode insert (D)**. While electrical energy applied by a TENS unit does only reach approximately 3 to 5 mm deep (A), a low impedance conduit (B) can conduct electrical energy to a location more distant inside the body to activate a nerve (C). The BASMATI insert is manufactured following similar procedures and from the same materials as the expected Target product, thus providing an assessment of the safety (primary objective assessed in this study) and interfacing efficacy (secondary objective) of the technology.

[2] Trevathan JK, Baumgart I, Nicolai EN, et al. A Truly Injectable Neural Stimulation Electrode Made From an In-Body Curing Polymer/Metal Composite. BioRxiv. 2019 BioRxiv https://doi.org/10.1101/584995.

Preclinical animal and benchtop work has been successfully conducted to prove out the technology. The conduit placement is designed to be very similar to a lidocaine injection pain physicians provide as part of their daily practice today, utilizing fluoroscopic or ultrasound visualization during the procedure. Using a needle of 2 to 5 mm diameter as a trocar, a wire rope is inserted to be in close proximity to the nerve at one end of the conduit, while the other ("current collector") end is left as a loop in the subcutaneous tissue. After closing the puncture wound with steri strips or sutures, the patient will be allowed to recover for a few days, allowing the injected conduit to stabilize. After a few days of recovery, electrical current to stimulate the nerve is applied on the outside of the skin with a TENS unit, from where it reaches the collector end just below the skin. Once the current reaches the collector end, it is transferred at a very low electrical impedance to the nerve target, providing the neuromodulation treatment.

The advantages of this solution are (1) that the signal generator is outside the body, eliminating the need for battery replacement surgeries and (2) that the puncture wound to place the conduit leaves a significantly smaller scar than current procedures to place neuromodulation electrodes, leads and signal generators.

This conduit represents an injectable electrode that is formed into its final shape inside the body, or Injectrode for short.

While Neuronoff, Inc. has tested all components of this system in preclinical benchtop and animal studies, including very successful long term biocompatibility studies of the actual Injectrode insert for up to 180 days, it was deemed to be in the best interest of study participants and the company to conduct the clinical work in **two subsequent clinical studies** that build on top of each other:

First a clinical study to document the safety and electrical interfacing efficacy of the Injectrode insert for up to 28 days. This early feasibility study focuses primarily on documenting biocompatibility by having the Injectrode insert placed just below the skin into the subcutaneous tissue. Based on extensive chronic work in animals a rejection reaction is not expected, but if it were to happen, would be very easily dealt with by explanting the small insert. After 28 days, a short electrical measurement would be used to confirm successful interfacing with the device just minutes prior to removal by a dermatologic surgeon. This study design allows for risk to be very minimal, enabling the NSR designation for this study. **The document in hand describes this first study.**

The second clinical study is designed to build on the knowledge of the successful first study and will evaluate the deployment of a longer version of the Injectrode insert from a subcutaneous location to a nerve at a depth of approximately one inch in depth measured from the skin. The second study thus represents an actual treatment efficacy study for a clinical condition. This second clinical study is a future study and **not** the one described in the document in hand.

1.4 Rationale for the non-significant risk classification of this study

While interfacing with a nerve at a depth of 2 to 3 cm would be a possibility for an early feasibility study, it was determined that a subcutaneous placement of the shortened study device would provide the same biocompatibility data and the same electrical transmission capabilities efficacy data, while subjecting the study participants to a very minimal and controlled amount of Non-Significant Risk (NSR).

Under 21 CFR 812.3(m), an NSR device study is one that does *not* meet the definition for an SR device study. Below we cover all criteria that define an SR device and then detail why the Basmati Injectrode does *not* meet these.

Specifically, as per 21 CFR 812.3(m), an SR device:

1. **Is intended as an implant and presents a potential serious risk to the health, safety, or welfare of a subject.**
   The commercial version of Neurnoff's Injectrode will be an implantable electrode. However, this early feasibility prototype is limited to 28 days of use to avoid risk resulting from long-term implantation duration where regular follow-up is impractical or impossible. Therefore, the Basmati insert does not meet the definition of an implant. In this study, the Basmati will be used to document the clinical biological response after a placement duration of 28 days only. According to FDA guidance, "Use of International Standard ISO 10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" (2013): a device that makes contact with tissue for a period of time less than 30 days poses considerably lower risk to patients.

2. **Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.**
   The Basmati Injectrode insert is not intended for use supporting or sustaining human life. In the proposed safety study, the device will be temporarily implanted subcutaneously for the purpose of confirming its biocompatibility compared to a previous animal study.

3. **Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject.**
   In the proposed safety study, the Basmati insert will be used as a passive device not intended for diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health. Prior to removing the device in a minimally invasive procedure, the Injectrode will be briefly interfaced with electrical current using standard electro-acupuncture techniques, following the labeling for these approved devices. The total time of exposure to this limited stimulation period will be approximately 20 minutes right prior to device extraction via Mohs procedure.

4. **Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.**
   Based on the Neuronoff, Inc. Quality Management System, risks associated with the device will be evaluated and addressed per the Design Control Procedure, SOP-02 and the Risk

Management Procedure, SOP-05 and according with the ISO-14971 Risk Management Standard to assure that the Basmati Injectrode insert is deemed to not represent any potential for serious risk to the health, safety, or welfare of a subject. The minimally invasive placement at a location in the subcutaneous tissue and rigorous follow-up schedule are designed to allow the physician to monitor the response of each study participant very closely and, if necessary, explant the device prior to the 28 day mark without unnecessary risk to the health, safety, or welfare of a subject. The material of the Injectrode is 99.99% gold, a material commonly used in neuromodulation electrodes that is bioinert and very well received by humans clinically. The method of removing the Injectrode at the end of the safety study will follow a procedure similar to a Mohs procedure, a standard clinical practice that poses little risk to study subjects. Subjects will be followed for signs of inflammation of the surgical site, granulomas, irritation.

This early feasibility study aims to document the clinical biological response to an Injectrode, roughly the size of a Basmati rice grain, placed temporarily into up to 10 healthy volunteers for a duration of up to 28 days. The efficacy of the device is assessed by measuring electrical and sensory nerve recruitment data immediately prior to explanting the device. These data are intended to provide rationale for a follow-up study testing a therapeutic intervention.

Risk to the study participant is further minimized by placing the study device subcutaneously with the option for a quick minimally invasive explant procedure before the 28 day mark if deemed necessary by the study PI.

This non-significant risk (NSR) study is the first of two early feasibility studies. This first NSR study is designed to subject the study participants to a minimal risk while collecting first human biocompatibility, electrical interface and neurostimulation data.

The expected data set is designed to enable a follow-up study investigating the placement of a longer Basmati-style Injectrode that ranges from the subcutaneous tissue to a nerve located at an approximate depth of 2 to 3 cm deep inside the body. The present BASMATI study mimics the placement into the subcutaneous tissue location and thereby provides the data to enable the follow-up study evaluating a longer Basmati-like electrode to be placed. To minimize risk for participants in the mentioned follow-up study, biocompatibility data and electrical interfacing data are collected in the first NSR study as described in the document in hand.

1.5 Comparison to earlier studies

The Basmati Injectrode will be placed subcutaneously in up to 10 healthy volunteers for a duration of up to 28 days. On the last day of the study, the Basmati Injectrode will be explanted with a margin of approximately 1mm of healthy tissue utilizing a Mohs surgical approach, ensuring maximal study participant safety while enabling the collection of histological samples for chronic human biocompatibility data. Just prior to explanting the device, two very small 30 gauge needles (similar to electro-acupuncture needles) will be placed approximately 5mm into the skin at the location of the subcutaneously placed Basmati, thereby forming an electrical interface with the Basmati. Electrical impedance and stimulation thresholds for subcutaneous afferences (sensory nerves) will be recorded with the two needles and a TENS electrode patch placed extracorporeally at a distance of approximately 10 cm from the Basmati location.

This approach is similar to that utilized with the StimRouter Neuromodulation System, which also consists of an implanted lead with external stimulation equipment to activate the lead transcutaneously [3] [4] [5]. Both systems utilize minimally invasive implantation techniques, with the probe injected via hollow stainless steel tubes[6] [7]. However, the Injectrode is different in that it is presented as a gold mesh as opposed to a fixed metal coil, which allows for improved in-body conforming and thus better reach of potentially hard-to-access anatomic targets. Also, in the least invasive use case, the Injectrode can be stimulated via an external TENS unit without requiring an implanted stimulation cable. Thus, the Injectrode offers improved placement potential and functionality with similar or lesser invasiveness than available technologies.

1.6 Study participant safety

Subject safety is our main priority. Accordingly, the devices chosen for this study were selected for their ability to minimize risk. Stimulation will be controlled using an FDA cleared Constant Current Stimulator (DS7A, Digitimer, USA). Impedance will be measured with a handheld, battery-powered oscilloscope (ScopeMeter, Fluke, USA) that is certified and calibrated. Percutaneous interfacing with the Injectrode will be achieved using standard clinical grade sterile 30 gauge needles.

1.7 Pre-clinical data / Summary of previous animal studies

Basmati style Injectrodes, in various sizes and shapes (ranging from 8x1x1mm to 12x5x2mm) have been placed successfully subcutaneously in 54 rodents (n=108 devices), for varying durations up to 180 days. No serious adverse events have occured. As such, a strong safety profile for the device, sterilization method, placement location, and biological response has been demonstrated. Percutaneous conductivity was also measured in these animals throughout the course of the device placement period. Surgical removal of the device in a survival procedure (4 weeks placed, removed, 4-8 weeks survival post removal) has also been completed for n=8 devices, also without any adverse events.

In a subset of the 108 devices, removal of the device was completed with the skin layer left intact, intended for histopathological analysis to assess the biological response to the device. A representative sample (n=30) was submitted to a third-party histopathologist (Nicholas P. Ziats, Case Western Reserve University). Two transverse sections of the subcutaneously placed devices were stained with either H&E and Trichrome, for placement periods of 4 (n=12), 8 (n=12), 12 (n=2), and 26 weeks (180

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[3] Deer TR, Levy RM, Rosenfeld EL. Prospective Clinical Study of a New Implantable Peripheral Nerve Stimulation Device to Treat Chronic Pain. Clin J Pain. 2010 Jun;26(5):359-72. https://doi.org/10.1097/AJP.0b013e3181d4d646

[4] Deer TR, Pope JE, Kaplan M. A novel method of neurostimulation of the peripheral nervous system: The StimRouter implantable device. Tech Reg Anes Pain Manag. 2012 Apr;16(2):113-117. https://doi.org/10.1053/j.trap.2013.02.007

[5] Deer T, Pope J, Benyamin R, Vallejo R, Friedman A, Caraway D, Staats P, Grigsby E, McRoberts WP, McJunkin T, Shubin R, Vahedifar P, Tavanaiepour D, Levy R, Kapural L, Medhail N. Prospective, Multicenter, Randomized, Double-Blinded, Partial Crossover Study to Assess the Safety and Efficacy of the Novel Neuromodulation System in the Treatment of Patients With Chronic Pain of Peripheral Nerve Origin. Neuromodulation. 2016 Jan;19(1):91-100: https://doi.org/10.1111/ner.12381

[6] Acute Human Study: StimRouter for Peripheral Nerve Stimulation of Discrete Peripheral Nerves (SimRouter). First Posted April 23, 2008. https://clinicaltrials.gov/ct2/show/NCT00665132?id=NCT00665132+OR+NCT01592344&draw=2&rank=2&load=cart

[7] Bioness® StimRouter™ Neuromodulation System for Chronic Pain Therapy. First Posted May 7, 2012. https://clinicaltrials.gov/ct2/show/NCT01592344?id=NCT00665132+OR+NCT01592344&draw=2&rank=1&load=cart

days, n=4). The complete histopathological report is included in the appendix (REC-020). The histopathologist drew the following conclusions:

There was normal fibrous capsule formation, with the most prominent finding being the expected inflammatory response to any implanted material. The fibrotic response was variable – some devices had a higher degree of inflammatory and foreign body giant cells than others. Responses range from +1 to +3 (mild to moderate) responses, the histopathologist stating that this range did not seem concerning and that he assumed it to simply be inter-subject variability. He cited the variable response of patients to COVID as a case-in-point. There was no evidence of adverse granuloma, necrosis (e.g., no acute toxicity), tumor formation or infection. More details are provided in the complete histopathological report that is included in the appendix (REC-020).

Below is a representative histological image (Trichrome Stained), identifying the fibrous capsule and small vasculature with red blood cells (RBCs). The small blood vessels are indicative of a well received implant with a thin fibrous capsule. The gold wires of the Basmati Injectrode are also pointed out, with an image of higher magnification showing the individual RBCs within the vascular lumen, along with collagen fibers - indicative of stable integration and a normal fibrotic response.

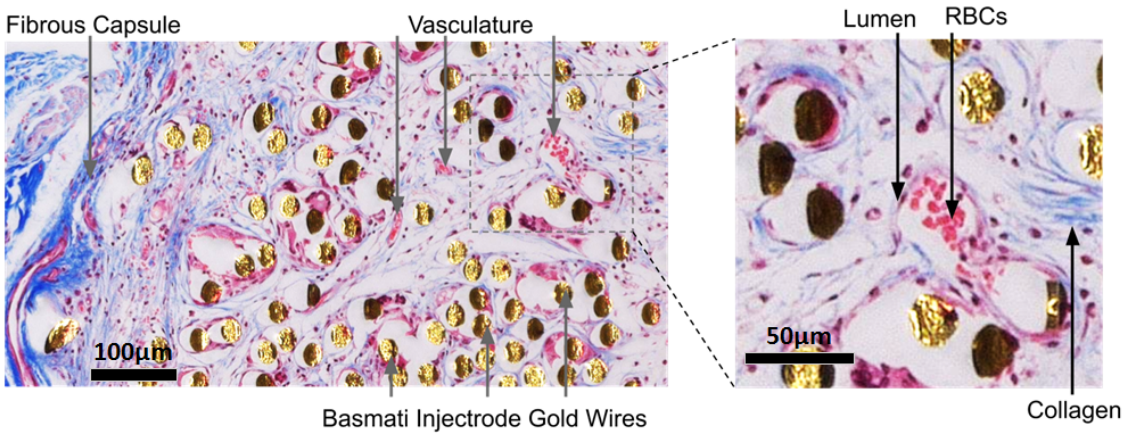

Figure 2: Representative histological image of a cross-section of the gold wires of an Basmati style Injectrode indicating key histological features (Fibrous Capsule, Vasculature - Lumen and Red Blood Cells). A higher magnification insert to the right shows a blood vessel lumen and RBS's, indicative of a readily integrated device.

2.0 OBJECTIVES

Success of this study is defined based on primary and secondary outcome measures. These are provided with greater detail below.

2.1 Primary Outcome Measures: Safety

Primary measures focus on device safety and will include the verification of the absence of unexpected inflammation and minimization of excessive encapsulation around the Injectrode as verified by cell staining and pathohistological analysis. Fluoroscopic imaging will be used to document positioning of the Basmati Injectrode lead.

2.2 Secondary Outcome Measures: Interfacing Efficacy

Secondary measures focus on device effectiveness. These will include impedance and stimulation threshold measurements for subcutaneous afferent nervous tissue.

3.0 DEVICE

3.1 Neuronoff Basmati Injectrode insert

This Clinical Non-Significant Risk (NSR) Study will focus on the placement, interfacing with and histopathological assessment of the Basmati Injectrode.

The Basmati Injectrode insert (figure 3) is a mesh formed from gold wire of 99.99% purity, a widely used material in medical devices, offering excellent biocompatibility combined with chemical, mechanical and electrical longevity when implanted into the human body[8] [9] [10] [11]. The conductive mesh is fabricated from wire with a nominal diameter of 25 microns and at a size of 4 mm width by 10 mm length at about 1.75 mm thickness. This size is similar to a cooked grain of basmati rice.

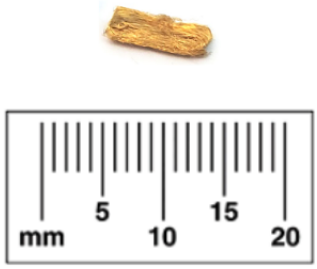

Figure 3: Basmati Injectrode insert is about the size of a grain of rice.

[8] Geddes, L.A., Roeder, R. Criteria for the Selection of Materials for Implanted Electrodes. *Annals of Biomedical Engineering* **31**, 879–890 (2003). https://doi.org/10.1114/1.1581292

[9] Hielm-Bjorkman A, Raekallio M, Kuusela E, Saarto E, Markkola A, Tulamo RM. Double-blind evaluation of implants of gold wire at acupuncture points in the dog as a treatment for osteoarthritis induced by hip dysplasia. *Vet Rec.* 2001;149(15):452-456. https://doi.org/10.1136/vr.149.15.452

[10] Product: Soft Tissue Marker, Composed of 99.95% Gold
https://www.accessdata.fda.gov/cdrh_docs/pdf3/k031206.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf9/K091645.pdf

[11] Product: Gold Eyelid Weight Implants, Composed of 99.99% Gold
https://www.accessdata.fda.gov/cdrh_docs/pdf/K971242.pdf
https://www.accessdata.fda.gov/cdrh_docs/pdf15/K150986.pdf

The Basmati Injectrode insert will be provided, loaded inside a delivery system to be attached to a standard 3mL luer lock Syringe. The Basmati Injectrode System Assembly (F-0001, see Figure 5A and 5B) is made of materials and components that are FDA listed from qualified suppliers, and will have limited duration of contact with study participant tissue. The materials along with all other device-contacting manufacturing materials are easily cleaned and sterilized following validated processes. The device assembly will be delivered clean, and sealed in a Steam sterilization tyvek pouch placed in a padded box with the appropriate labels. The device will be sterilized using a recommended and validated steam sterilization cycle. The Basmati Injectrode will be placed into the body by a cannula-based delivery device following a stab incision. Removal of the retaining clip (C-0002) readies the device for injection from the cannula (C-0001) into the surgical site.

Figure 4: Basmati Injectrode System Assembly in a sterilization pouch (without label)

During the surgical procedure, the Basmati Injectrode is ejected from the delivery device after introducing the cannula into a subcutaneous tunnel first created by blunt dissection. Creating the skin opening with sharps, a channel via blunt dissection and deploying the Basmati Injectrode is a procedure that can be achieved in under 10 minutes of surgical time.

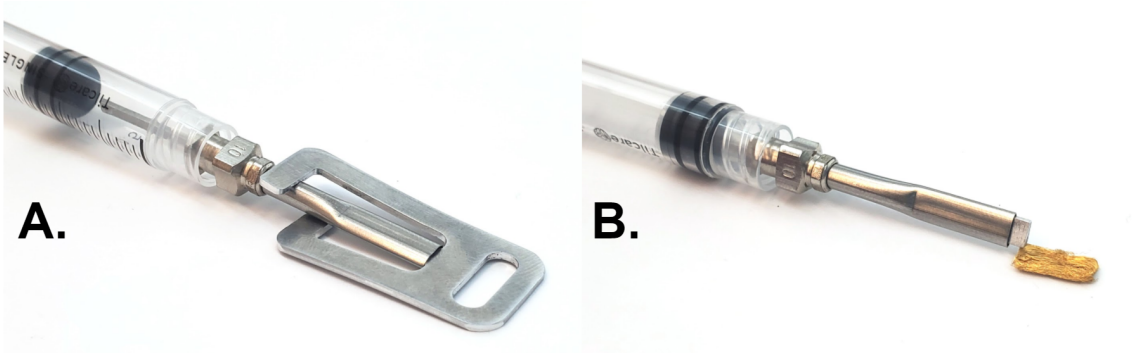

Figure 5: Delivery device attached to a standard 3mL syringe (A) and the Basmati Injectrode ejected from the delivery device (B)

The Basmati Injectrode™ is indicated for the investigational use for the assessment of chronic biocompatibility, electrical interfacing and neurostimulation data in humans. The investigational devices used for this study will be sourced from Neuronoff, Inc. and a list of all components is provided in the appendix.

3.2 Regulatory Classification

The Neuronoff, Inc Basmati Injectrode™ is an investigational device and is not yet classified. However, similar devices (i.e. StimRouter) are identified as Class II by the US FDA.

The sponsor has determined that this qualifies as an early feasibility study of non-significant risk.

4.0 STUDY DESIGN

The proposed study is a prospective, single-center, single-arm, non-randomized design. The study will screen up to 20 subjects for study eligibility and potential enrollment. Up to 10 study participants will be provided with the placement of a Basmati Injectrode insert. The maximal placement duration will be 28 days. Subjects selected to participate in the trial will be solely healthy volunteers without any preexisting condition indicated for treatment. Each subject will be followed during the trial period of approximately 45+/-2 days.

The study will end when the last subject has completed the trial period and exited. The expected enrollment period for this study is approximately 2 months. After exit from the clinical study, subjects will continue to be followed by their physician per standard of care. All device and procedure-related AEs and UPs will be collected and reported per the study protocol.

4.1 Schedule of Events (SOE)

Assessments and Data Collection	Screening and Enrollment	Call for patch removal	Injectrode Placement	Follow-up visits	Efficacy and Explant visit	Post study follow-up
Day (relative vs. Placement)	-5 to -4	-2	0	7 ± 2 14 ± 2	28 (-2 to 0)	48 ± 2
● Eligibility confirmation	✓					
● Medical history ● Physical exam	✓ ✓					
● Informed consent	✓					
● Record demographics ● Verification of absence of allergy to gold & pregnancy test ● Confirmation of study eligibility	✓ ✓ ✓					
● Gold skin patch test placement	✓					
● Removal of skin patch		✓				
● Read skin test patch results			✓			
● Basmati placement procedure ● Ultrasound & Fluoroscopy image capture			✓ ✓		✓ (pre & post)	(✓)
● Recording of images of surgical site / placement location ● Remove skin suture(s) if placed during surgery	✓		✓ (post)	✓ (✓)	✓	✓ (✓)
● Measure impedance needle to needle connection ● Measure stimulation thresholds ● Removal procedure ● Study participant exit					✓ ✓ ✓	✓

Table 1: Assessments and data collection

5.0 OUTCOMES

The outcomes of the study are focused on collecting data to determine clinical outcomes of placing the Basmati Injectrode for up to 28 days in healthy study participants to 1) assess tissue responses and, on the last day just prior to explant, 2) collect data describing the quality of the electrical interfacing with the Injectrode from outside of the body, as well as with subcutaneous sensory nerves surrounding the Injectrode insert.

Safety data will also be collected at all visits. Data will be collected using:

- True color images of the surgical site and the insert placement location.
- Ultrasound and fluoroscopy (x-ray) images of the insert placement location.
- CRFs to capture any pain or discomfort, AEs and UPs.
- Patho-histological data from tissue samples collected during the explant procedure (Injectrode with approximately 0.5 to 1mm of naïve tissue in Mohs style procedure).

5.1 PRIMARY SAFETY OUTCOME MEASURES

Primary measures of device safety will include verification of the absence of unexpected inflammation and minimization of excessive encapsulation around the Injectrode as verified by cell staining and pathohistological analysis. Fluoroscopic imaging will be used to document positioning of the Basmati Injectrode lead.

5.2 SECONDARY SAFETY OUTCOME MEASURES

Secondary measures of device effectiveness will include impedance and stimulation threshold measurements for subcutaneous nervous tissue.

6.0 MINIMIZATION OF BIAS

Potential sources of bias in this study may result from selection of subjects, and evaluation of study data. The following methods have been incorporated into the study to minimize potential bias: Subjects will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment. Subject demographics will be collected at baseline on possible differences that may affect the primary objective. All study clinicians, participating site personnel, and the Sponsor's personnel will be trained on their respective aspects of the study using standardized training materials. All study clinicians will be trained on and required to follow the Clinical Investigation Plan.

7.0 INVESTIGATORS

7.1 INVESTIGATOR SELECTION AND RESPONSIBILITIES

In order for the Investigators to participate in the study, they must provide a Curriculum Vitae (CV) demonstrating evidence of sufficient training and experience in the management of study participants with chronic pain. The Investigator's participation in other clinical studies must not present a conflict of interest and will not interfere with the clinical study enrollment, study management or study confidentiality. Each participant must be willing to provide any conflicts of interest details, and must be willing to comply with all federal laws and regulations as well as IRB rules regarding clinical studies.

8.0 STUDY POPULATION

The study will recruit healthy volunteers that pass a thorough general medical exam. Subjects may either be male or female and must meet all of the study's eligibility criteria, which are typical eligibility criteria for early feasibility studies. They will be required to sign an informed consent form prior to being asked to participate in the study, undergoing any study-related procedures or having any data collected. It is expected that up to 20 subjects may be screened to be enrolled based on eligibility, and up to 10 subjects will undergo minimally invasive surgery to implant the Basmati Injectrode.

8.1 Inclusion Criteria

To be eligible for this study, study participants ***MUST***:

1. Sign a valid, Institutional Review Board (IRB)-approved informed consent form (ICF) and understand the study requirements.
2. Be 18 years of age or older when written informed consent is obtained.
3. Be in good physical and mental health as assessed by a general practitioner.
4. Be able to tolerate electrical stimulation (TENS).
5. Be willing and able to understand and comply with all study-related procedures during the course of the study.

8.2 Exclusion Criteria

To be eligible for this study, study participants ***MUST NOT***:

1. Have a cognitive impairment or exhibit any characteristic that would limit the study candidate's ability to completely understand and sign a valid, IRB-approved informed consent form.
2. Have a positive pregnancy test (conducted during enrollment).
3. Have a positive Allergic reactivity to Gold skin test (conducted during enrollment).
4. Show symptoms indicative for Covid19 as assessed during enrollment.
5. Have a skin condition at the planned surgical location.
6. Have a blood coagulation disorder or other indication with the potential to impact the study biocompatibility data in unpredictable ways.
7. Have a medical condition that is a contraindication for minimally invasive surgery.
8. Be implanted with a cardiac defibrillator or pump.
9. Have a history of cardiac arrhythmia with hemodynamic instability
10. Be implanted with a neurostimulator.
11. Have any active electrical implant of any other kind.

12. Have metal implants (particularly in hip).
13. Have active infection.
14. Have allodynia.
15. Take regular use of antiplatelet medications (e.g. aspirin, ticlopidine (Ticlid), clopidogrel (Plavix), tirofiban (Aggrastat) or eptifibatide (Integrilin)).
16. Have untreated drug habituation or dependence.
17. Have uncontrolled seizures (averaging > 2 seizures per month).
18. Currently require, or be likely to require, diathermy and/or MRI during study duration.
19. Have a history of adverse reactions to local anesthetics (e.g. lidocaine).

8.3 Sample Size

The study sample size is limited to 10 subjects receiving the Basmati Injectrode insert.

9.0 Methods and Procedure

9.1 DATA COLLECTION REQUIREMENTS

Subject data will be collected and documented on case report forms (CRFs). Templates of the CRFs for this study are located in Appendix 17.

9.1.1 Subject Screening Procedure

Subjects will be chosen from healthy volunteer candidates. Potential study participants must pass a thorough general medical exam. Subjects may either be male or female and must meet all the study's eligibility criteria which are typical eligibility criteria for early feasibility studies. They will be required to sign an informed consent form prior to being asked to participate in the study, undergoing any study-related procedures or having any data collection occurring.

Assessments and Data Collection	**Screening and Enrollment**	Call for patch removal	Injectrode Placement	Follow-up visits	Efficacy and Explant visit	Post study follow-up
Day (relative vs. Placement)	**-5 to -4**	-2	0	7 ± 2 14 ± 2	28 (-2 to 0)	48 ± 2
• Eligibility confirmation	✓					
• Medical history • Physical exam	✓ ✓					
• Informed consent	✓					
• Record demographics • Verification of absence of allergy to gold & pregnancy test • Confirmation of study eligibility	✓ ✓ ✓					
• Gold skin patch test placement	✓					
• Removal of skin patch		✓				
• Read skin test patch results			✓			
• Basmati placement procedure • Ultrasound & Fluoroscopy image capture			✓ ✓		✓ (pre & post)	(✓)
• Capture of images of surgical site • Remove skin suture(s) if placed during surgery	✓		✓ (post)	✓ (✓)	✓	✓ (✓)
• Measure impedance needle to needle connection • Measure stimulation thresholds • Removal procedure • Study participant exit					✓ ✓ ✓	✓

Table 2: Focus on Screening and Enrollment

9.1.2 Informed Consent

Informed consent is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative's or guardian's) voluntary agreement to participate in a particular clinical investigation after information has been given to the subject on all aspects of the clinical investigation relevant to the subject's decision to participate. When a subject signs and dates the informed consent form, he/she is considered a subject enrolled in the study.

Prior to initiation of any study-specific procedures, subjects (or their legally authorized representative or guardian) must sign and date the informed consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization, or equivalent, where required by law and IRB. Documentation that consent was obtained prior to any study-related procedures must be maintained in the subject's case history.

9.1.3 SCREENING and ENROLLMENT VISIT (IN-PERSON, day -5 or day -4)

Once the informed consent has been documented, the study participant's eligibility for study participation is verified at the Enrollment Visit. During this assessment, the study physician will collect and document each potential participant's relevant medical history (including diagnosis), demographics and physical examination results. The visit concludes with the placement of the allergy skin test patch on the arm of the study participant. The gold allergy skin test patch is essentially a small band-aid filled with gold salt. According to the test's instruction for use, the patch must be placed on the skin for two to three days prior to an additional waiting period of two more days before the skin reaction can be interpreted by the physician. Accordingly, the next two visits are scheduled with the study participant as (1) a phone call to remove the skin test while creating a record in the corresponding CRF (see 9.1.4 below) and the (2) actual in-person Insert Placement Visit with a two-day delay following the phone call.

9.1.4 ALLERGY TEST PATCH REMOVAL VISIT (CALL, day -2)

The first follow-up visit is a phone call scheduled for two (three) days after the Enrollment Visit. The study participant is asked to remove the gold allergy skin test patch and a record of the removal is made in the corresponding CRF for that visit. The scheduling of the Insert Placement Visit for two days later is verified with the study participant.

9.1.5

9.1.6 INSERT PLACEMENT VISIT (IN-PERSON, day 0)

The Insert Placement Visit begins with an examination of the study participant's arm to capture and interpret the result of the gold allergy skin test by the physician. Once the absence of a gold allergy is verified, the participant advances to the group of up to 10 participants that will receive the Basmati Injectrode insert.

Appropriately trained field staff will assist as necessary with the Basmati Injectrode insert procedure. The recommended placement location for the device on the left or the right hip region (figure 6) will be determined by the physician and documented on the CRF.

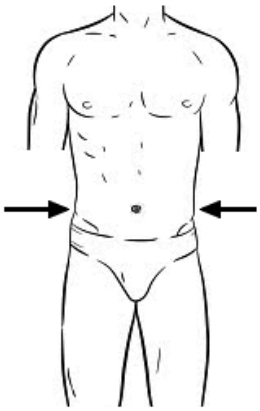

Figure 6: Depiction of the surgical location (arrows). Placement of the Basmati Injectrode is the hip region of the study participant at approximately the height of the naval.

Prior to the placement of the insert, the surgical location near the hip, approximately at the height of the naval, is cleaned and sterilized following standard OR procedures (betadine, 70% isopropyl alcohol). Following an injection of subcutaneous lidocaine (1%), a small (~5mm) incision is made using a scalpel followed by blunt dissection of the subcutaneous tissue. Blunt dissection technique is used to create a tunnel of about 3-5 mm diameter, at a depth of approximately 2mm measured from the surface of the skin, and up to 2 cm long (**figure 7, A**).

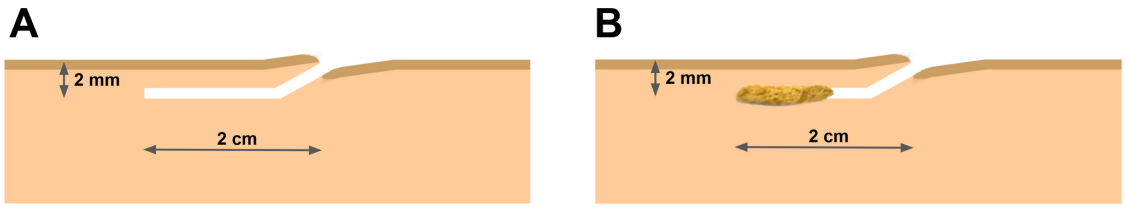

Figure 7: Approximate dimensions of the tunnel placed at the hip region prior to (A) and following (B) the placement of the Basmati Injectrode insert.

Using the deployment device, the Basmati Injectrode is placed into the distal end of the tunnel, leaving a length of approximately 1 cm of empty tunnel between the Basmati and the skin incision (**Figure 7, B**). At the clinician's discretion, pressure to the wound channel alone or surgical glue may be used to ensure proper adherence of the tunnel walls to close the length of the tunnel. The skin incision may be

closed with steri-strips, surgical glue or one or more small suture loops as per the physician's discretion.

Pain management will be provided post surgery based on physician discretion.

Information regarding the devices used, location and procedure data will be collected on an Insert placement section of the CRF. With the study participant's and the surgeon's consent, Neuronoff's representative may be present during the insert procedure.

The steps taken during the Injectrode Placement Procedure vist are further outline in the table below:

Assessments and Data Collection	Screening and Enrollment	Call for patch removal	**Injectrode Placement**	Follow-up visits	Efficacy and Explant visit	Post study follow-up
Day (relative vs. Placement)	-5 to -4	-2	**0**	7 ± 2 14 ± 2	28 (-2 to 0)	48 ± 2
● Eligibility confirmation	✓					
● Medical history ● Physical exam	✓ ✓					
● Informed consent	✓					
● Record demographics ● Verification of absence of allergy to gold & pregnancy test ● Confirmation of study eligibility	✓ ✓ ✓					
● Gold skin patch test placement	✓					
● Removal of skin patch		✓				
● Read skin test patch results			✓			
● Basmati placement procedure ● Ultrasound & Fluoroscopy image capture			✓ ✓		✓ (pre & post)	(✓)
● Capture of images of surgical site ● Remove skin suture(s) if placed during surgery	✓		✓ (post)	✓ **(✓)**	✓	✓ (✓)
● Measure impedance needle to needle connection ● Measure stimulation thresholds ● Removal procedure ● Study participant exit					✓ ✓ ✓	 ✓

Table 3: Focus on the Injectrode Placement visit

9.1.7 FOLLOW-UP VISITS (IN-PERSON or CALL, day 7 and day 14)

Follow-up visits will occur on day 7 (+/–2) and 14 (+/–2) post-procedure. Data collected at these visits will be recorded on case forms (CRFs) and will include the bolded (grayed) portion:

Assessments and Data Collection	Screening and Enrollment	Call for patch removal	Injectrode Placement	**Follow-up visits**	Efficacy and Explant visit	Post study follow-up
Day (relative vs. Placement)	-5 to -4	-2	0	**7 ± 2** **14 ± 2**	28 (-2 to 0)	42 ± 2
● Eligibility confirmation	✓					
● Medical history ● Physical exam	✓ ✓					
● Informed consent	✓					
● Record demographics ● Verification of absence of allergy to gold & pregnancy test ● Confirmation of study eligibility	✓ ✓ ✓					
● Gold skin patch test placement						
● Removal of skin patch		✓				
● Read skin test patch results			✓			
● Basmati placement procedure ● Ultrasound & Fluoroscopy image capture			✓ ✓		✓ (pre & post)	(✓)
● Capture of images of surgical site ● Remove skin suture(s) if placed during surgery	✓		✓ (post)	✓ **(✓)**	✓	✓ (✓)
● Measure impedance needle to needle connection ● Measure stimulation thresholds ● Removal procedure ● Study participant exit					✓ ✓ ✓	 ✓

Table 4: Focus on follow-up visits

9.1.8 EFFICACY & EXPLANT VISIT (IN-PERSON, day 28)

This visit has two parts. The total duration of this visit is expected to be approximately 1 hour.

The first part of the visit is focused on capturing stimulation thresholds of cutaneous afferent nerves to provide information about the Injectode's capabilities to conduct current at low electrical impedance values. This first part is anticipated to last for approximately 30 minutes and scheduled to occur just before the explant of the Basmati Injectrode insert.

The second part of the visit is the actual explant of the device that will then be sent to histopathology for further processing. This second part is anticipated to last for approximately 30 minutes and will include image capturing for purposes of documentation.

Part I: Impedance and stimulation threshold data acquisition

Materials:

Stimulation will be provided using a DS7A Constant Current Stimulator unit (Digitimer), a device with CE and FDA clearance. Electrical impedance will be measured with a handheld, battery-powered oscilloscope (Fluke ScopeMeter) that is certified and calibrated. Sterile clinical grade standard needles intended for single patient use (30 gauge) will be used to directly interface percutaneously with the Injectrode. Details for this interfacing approach are provided below. A clinical grade, disposable, surface patch electrode will be used as a distal return, referred to as a TENS electrode/patch in this document. The Stimulator, Oscilloscope, Needles and TENS electrodes will be connected together using standard leads (Pamona, Comed).

Methods:

The setup for these stimulation and impedance tests are done under two types of visualization. First, visualization is done via ultrasound according to a Mohs' surgery plan. Second, the setup is visualized with fluoroscopy to ensure that the needles are placed precisely within the subcutaneously implanted Basmati Injectrode.

All equipment will be turned on prior to use, followed by connecting the Stimulator in parallel to the Oscilloscope as shown in Figures 7a through 7e below. Data will be recorded for every measurement. Prior to beginning the measurements, test leads will also be hooked up to the stimulator in parallel. Generally, measurements during this visit will be recorded at a current amplitude ranging between 0.1 and 10 mA and pulse widths ranging from 50 µsec to 1500 µsec. Reference impedance values will be recorded at a current amplitude at 1mA and a pulse width of 200 µsec using a reference resistor of 1 kOhm. The sensory stimulation thresholds ("Measurement 1" through "Measurement 3.3") below will be conducted with a preferred pulse width of 100 µsec and 200 µsec, and, if need be, may be measured once more with a different pulse width in the range between 50 µsec to 1500 µsec to be able to capture stable measurements.

In order to record sensory afferent nerve responses to electrical stimulation, it is imperative that lidocaine is not injected at the site of the Injectrode for the entity of part 1. Instead, the skin above the

Injectrode is cleaned using 70% Isopropyl alcohol at the site of the Injectrode with a margin of 3cm around the site, identified via palpation of the skin. Two 30 gauge needles are inserted through the cleaned skin into the Injectrode as shown in Figures 8a through 8e. At a location 1-2cm away from the Injectrode, a third 30 gauge needle will be inserted as shown in Figure 8a. Finally, at a location approximately 10 cm away from the Injectrode, a TENS patch electrode will be placed to function as the return electrode for electrical current. Test leads with hooked ends will be attached to the needle shaft extending out of the skin and taped to the skin to keep the leads secure and from pulling on the needles should the study participant or lead move.

Measurement 1: Once the leads are properly attached to the needles and TENS patch, testing may commence. The first measurement will establish the stimulation activation (sensation) threshold of afferent nerves in the skin of the hip region of the study participant in the vicinity of where the Injectrode is present. Needle D and TENS patch C will first be connected to the stimulator (as shown in figure 8a), and step wise increments in stimulus amplitude will be performed until the study participant notes that they can perceive the stimulation (e.g. step size amplitude = 100 µA, pulse width = 200 µsec). The study participant will be asked to report when they perceive a paresthesia, essentially a tingling sensation of the skin. The current and pulse width values for the initial report of paresthesia will be recorded and may be verified with a second measurement. The values allowing the study participant to perceive a tingling paresthesia sensation are expected to be an order of magnitude smaller than currents needed to cause the perception of pain. If the study participant reports pain during the stimulation then the clinician will adjust their testing approach accordingly to avoid such participant feedback. Once the stimulation activation threshold is determined, lead D may be unplugged and needle D removed from the skin.

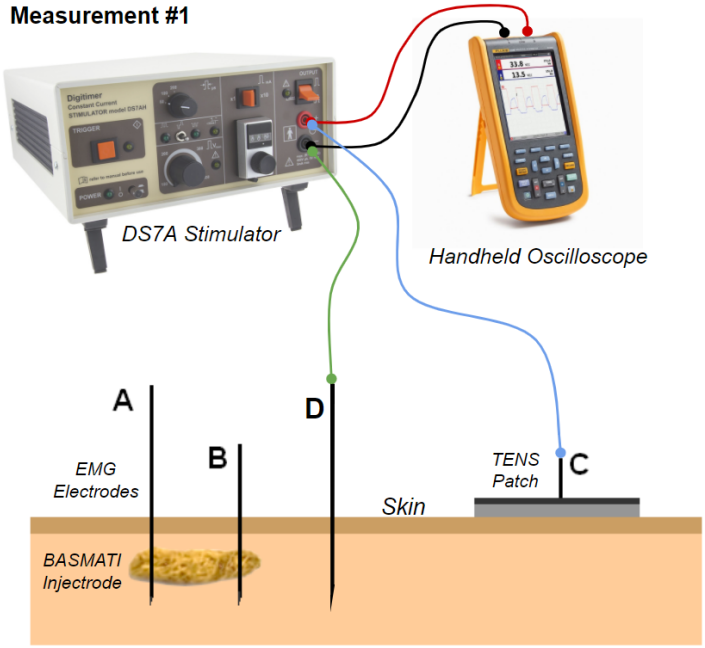

Figure 8a: Stimulus activation setup of electrodes for measurement #1.

A series of three stimulation tests will be performed between the Injectrode (A, B) and the TENS patch (C), as shown in Figures 8c, 8d, and 8e. The first stimulation for each measurement will be performed at or below the stimulation threshold established in measurement 1 for the study participant. The study participant will be asked whether they sensed the stimulus, and their answer recorded. If needed, the stimulation current will be increased in increments of 100 µA of current or 50-100 µsec of pulse duration until the study participant perceives the stimulus.

In **measurement 2** (Figure 8b), needle A and the TENS surface patch electrode (C) will be hooked up to the stimulator and oscilloscope.

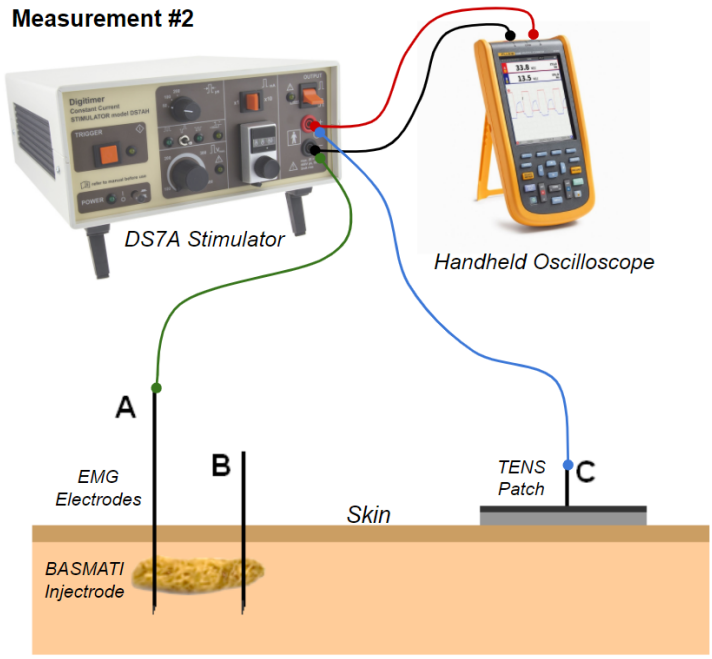

Figure 8b: Impedance and Stimulation setup of electrodes for measurement #2.

In **measurement 3** (Figure 8c), needle B and the TENS surface patch electrode (C) will be hooked up to the stimulator and oscilloscope.

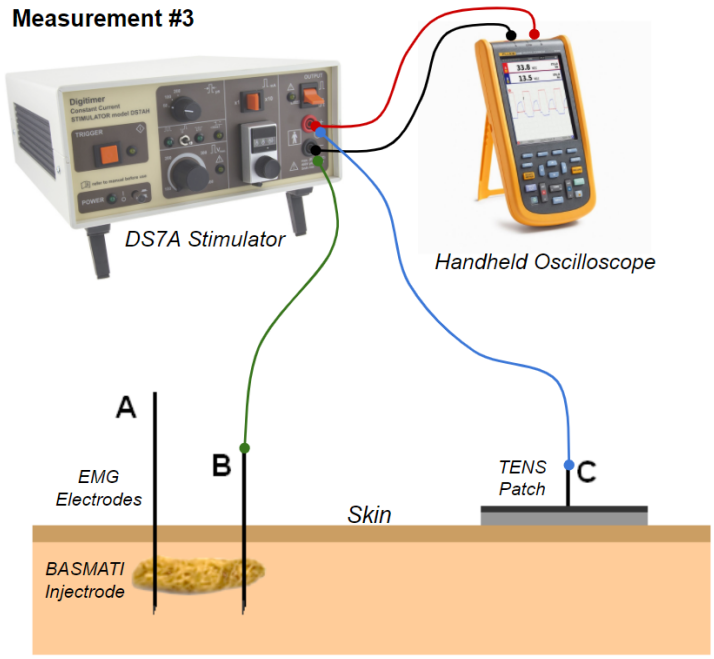

Figure 8c: Stimulation setup of electrodes for measurement #3.

In **measurement 4** (Figure 8d), needles A and B will be connected together to one output/input, while the TENS surface patch electrode (C) will be hooked up to the other output/input of the stimulator and oscilloscope.

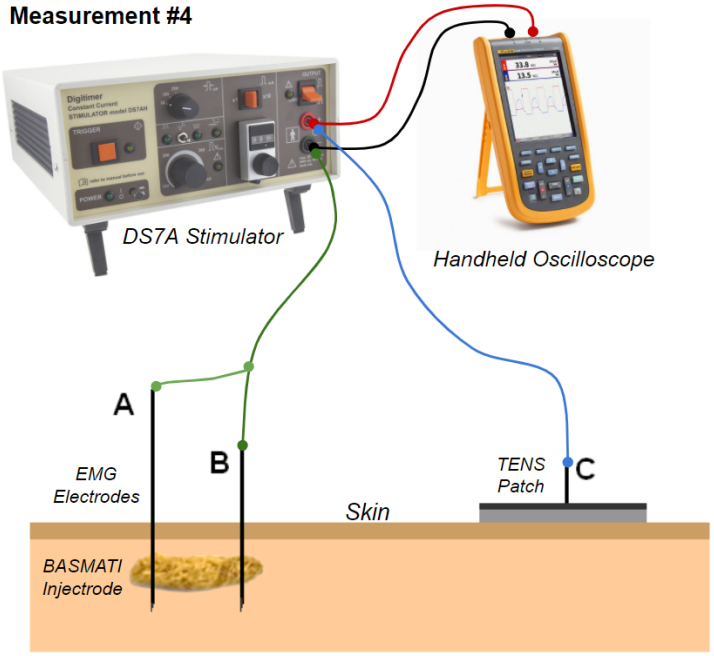

Figure 8d: Stimulation setup of electrodes for measurement #4.

Measurement 5: Lastly, needles A and B will be hooked up to the stimulator as shown in Figure 8e. Electrical stimulation at the stimulus activation threshold will be applied. The study participant will be asked if they still perceive the stimulation at threshold. If they do not, another stimulus activation threshold test will be performed (e.g. step size amplitude = 100 µA, pulse width = 200 µsec) up to 10 mA of current. After each stimulation, the study participant will be asked if they perceived the stimulation, with perception noted as the stimulus activation threshold of current passing through the injectrode. It is expected that the threshold in Measurement 5 will be at least five times higher than that recorded in Measurement 1, as a result of the conductive injectrode shunting (short-circuiting) current between the two needles, thus making it harder to stimulate nerves near the Injectrode. Recorded data from the oscilloscope will be used to calculate the impedance of the Basmati Injectrode.

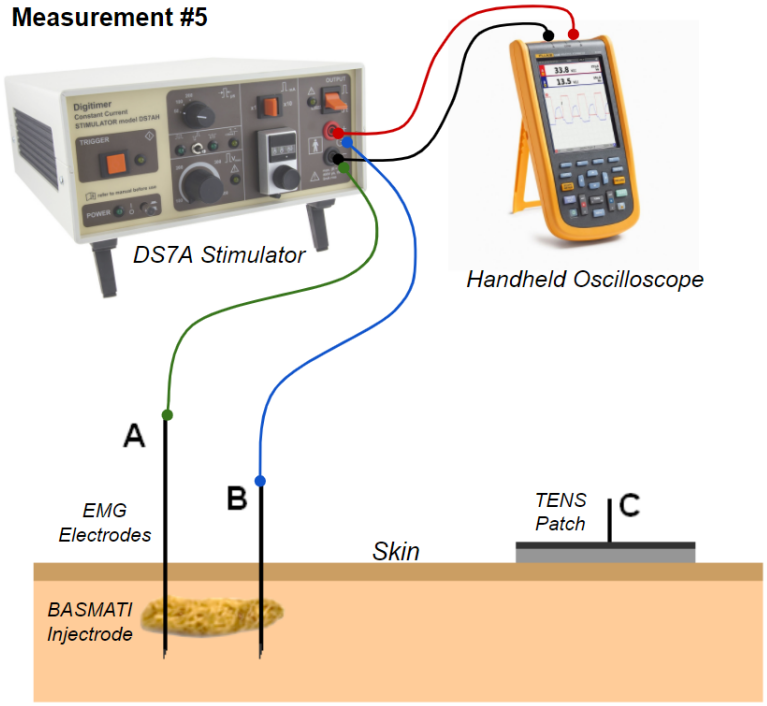

Figure 8e: Stimulation setup of electrodes for measurement #5.

The resulting table of amplitudes and pulse widths resulting from each measurement will be recorded in the CRF.

This closes part 1 of the efficacy and explant visit. The skin at the location of the Injectrode will now be cleaned once more and prepared for surgical removal of the Basmati Injectrode insert.

Part II: Explant (Device Removal)

Methods:

The explant surgical plan will be verified with images from ultrasound and fluoroscopy taken earlier the same day. The explant is a Mohs style surgery. The injection site is anesthetized via lidocaine (solution 1%), and a sharp cut is made above the Basmati Injectrode. Next, tissue forceps are used to hold onto the device while dissection is performed around the Injectrode in naïve tissue at a target distance of about 0.5 to 1 mm.

Once removed, the explanted Basmati Insert is placed in a glass vial containing Formalin (10% formaldehyde solution), labeled in code with sequential numbers for each study participant in compliance with HIPAA requirements. The subsequent wound is closed, in layers if applicable. The incision is closed with steri-strip, surgical skin glue or sutures as per the surgeon's discretion. The closed wound is then bandaged as per standard protocol.

At no time from explant to histological analysis report generation will Neuronoff, Inc. be in possession of the device, samples, or data. The device will be left in Formalin for 24 hours, at which time the solution will be exchanged for 70% ethanol by the clinical site. The fixed samples will then be shipped to the following location, with email notifications to Jennifer Mikulan (CWRU Tissue Resource Core, jjm10@case.edu) containing the subject "BASMATI Sample Submission" along with shipping tracking information and subject de-identified sample number:

CWRU Tissue Resource Core
Attn: Jennifer Mikulan
2058 University Hospitals Drive
Wearn Bldg. Rm #333
Cleveland, Ohio 44106

Histological slides generated by the Tissue Resource Core will then be transferred to an independent third party pathologist (Nicholas P. Ziats, Case Western Reserve University) for analysis and report generation. Once completed, the report and samples will be sent to Neuronoff, Inc. for safekeeping.

Upon completion of the explant, the site once occupied by the Injectrode is again visualized with ultrasound, and then again with fluoroscopy. Both visualizations will be documented.

Summary:

Assessments and Data Collection	Screening and Enrollment	Call for patch removal	Injectrode Placement	Follow-up visits	**Efficacy and Explant visit**	Post study follow-up
Day (relative vs. Placement)	-5 to -4	-2	0	7 ± 2 14 ± 2	**28 (-2 to 0)**	42 ± 2
● Eligibility confirmation	✓					
● Medical history ● Physical exam	✓ ✓					
● Informed consent	✓					
● Record demographics ● Verification of absence of allergy to gold & pregnancy test ● Confirmation of study eligibility	✓ ✓ ✓					
● Removal of skin patch		✓				
● Read skin test patch results			✓			
● Basmati placement procedure ● **Ultrasound & Fluoroscopy image capture**			✓ ✓		✓ (pre & post)	(✓)
● **Capture of images of surgical site** ● **Remove skin suture(s) if placed during surgery**	✓		✓ (post)	✓ (✓)	✓	✓ (✓)
● **Measure impedance needle to needle connection** ● **Measure stimulation thresholds** ● **Removal procedure** ● **Study participant exit**					✓ ✓ ✓	✓

Table 5: Focus on Explant visit

9.1.9 POST-EXPLANT VISIT & STUDY EXIT (IN-PERSON, day 42 +/- 2)

A Study Exit CRF must be completed for any subject who signed an informed consent form, as they are considered enrolled in the study. Data to be collected at this visit include study exit date and reason for study exit, device or procedure related AEs, technical observations/device deficiencies and surgical interventions.

Some scenarios may lead to study exit and require completion of a Study Exit CRF: These include subject ineligibility for the implant in the opinion of the study physician, failure to meet inclusion criteria, meeting exclusion criteria, removal of the SCS lead without re-implantation, attempted implant without SCS implantation, voluntary withdrawal by the subject, subject withdrawal by the investigator, failure to maintain adequate study compliance and/or subject death.

Assessments and Data Collection	Screening and Enrollment	Call for patch removal	Injectrode Placement	Follow-up visits	Efficacy and Explant visit	**Post study follow-up**
Day (relative vs. Placement)	-5 to -4	-2	0	7 ± 2 14 ± 2	28 (-2 to 0)	**42 ± 2**
● Eligibility confirmation	✓					
● Medical history ● Physical exam	✓ ✓					
● Informed consent	✓					
● Record demographics ● Verification of absence of allergy to gold & pregnancy test ● Confirmation of study eligibility	✓ ✓ ✓					
● Removal of skin patch		✓				
● Read skin test patch results			✓			
● Basmati placement procedure ● **Ultrasound & Fluoroscopy image capture**			✓ ✓		✓ (pre & post)	**(✓)**
● **Capture of images of surgical site** ● **Remove skin suture(s) if placed during surgery**	✓		✓ (post)	✓ **(✓)**	✓	✓ **(✓)**
● Measure impedance needle to needle connection ● Measure stimulation thresholds ● Removal procedure ● **Study participant exit**					✓ ✓ ✓	 ✓

Table 6: Focus on Post study follow-up

10.0 ADVERSE EVENT REPORTING

During the study, the investigator will determine whether any adverse events (AE's) have occurred. For the purpose of this protocol, an adverse event is any undesirable clinical occurrence in a subject that can be attributed to the device or incision closure procedure.

10.1 ADVERSE EVENTS

In this study, study participants should be encouraged to report AE's spontaneously or in response to general, non-directed questioning (e.g., "How has your health been since the last visit?") per Neuronoff SOP-38. Any time during the study, the study participant may volunteer information about any event that resembles an AE. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the CRF.

The following categories of adverse event severity are to be used:

Mild	Awareness of a sign or symptom that does not interfere with the study participant's usual activity or is transient, resolved without treatment and with no sequelae
Moderate	Interferes with the study participant's usual activity
Severe	Any fatal or immediately life-threatening clinical experience that requires a subject to be hospitalized, or hospitalization is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated. This includes events that cause fetal distress, fetal death, congenital abnormality or malignancy or any permanently disabling event.

Table 7: Categories of adverse event severity

10.2 ANTICIPATED ADVERSE DEVICE EFFECTS

The following ANTICIPATED EVENTS have been identified as possible complications of participation in the study.

- Infection at implant site
- Pain at implant site
- Bleeding
- Bruising
- Itch
- Allergic reaction

To minimize the risk of any study participant developing an allergic reaction to the Basmati insert's sole material (gold of 99.99% purity), a gold skin test will be performed during the first study visit. Patients only advance to the implant visit after a negative skin allergy test to gold has been confirmed.

10.3 UNANTICIPATED ADVERSE DEVICE EFFECTS

Unanticipated adverse device effects are defined as 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 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.

For the purposes of this study, serious is defined as any significant adverse experience, including those which may be either life-threatening or involve permanent or long term injuries, but excluding injuries that are non-life-threatening and that are temporary and reasonably reversible.

An Investigator must submit to the sponsor and to the responsible Medical Ethics Committee (IRB) any unanticipated adverse device effects that occur during the study as soon as possible, but in no circumstances later than ten (10) working days after the Investigator first learns of the effect.

Mild	Submit to IRB per local reporting requirements.
Moderate	Submit as soon as possible but no later than 10 working days after the Investigator first learns of the event.
Severe	Submit as soon as possible but no later than 10 working days after the Investigator first learns of the event, or per local reporting requirements, whichever is more conservative.

Table 8: Categories of adverse event severity and triggered processes

Contact Name:

Amol Soin, MD
Ohio Pain Clinic
7076 Corporate Way
Dayton, OH 45458

The study investigator adverse event reports are listed in Table 9 below:

Report	Submit To	Description/Contraints
Death	Sponsor	Submit as soon as possible but no later than 10 working days after the Investigator first learns of the event.
	IRB	Submit to IRB per local reporting requirements
Unanticipated adverse device effect (UADE)	Sponsor	Submit as soon as possible but no later than 10 working days after the Investigator first learns of the event.
	IRB	Submit as soon as possible but no later than 10 working days after the Investigator first learns of the event
Other Adverse Device Effects	Sponsor	Submit or report as required per local reporting requirements.
	IRB	Submit or report as required per local IRB reporting requirements.
	Regulatory Body	Submit or report as required per regulations.

Table 9: Investigator adverse event reports

11.0 STATISTICS

11.1 Study Population

All study participants who received treatment will be included in a statistical analysis. Any protocol deviations will also be reported.

11.2 Observational Pilot Study

As this is a first in human pilot study, this study will not be powered for statistical analysis. Instead, a representative number of 10 participants will be selected.

12.0 ETHICS

12.1 Medical Ethics Committee (IRB) Review

Prior to initiation of the study, the Principal Investigator (PI) will submit the study protocol, sample Informed Consent Form and any other documents that may be requested by the IRB for review and approval. The PI will request that the IRB provide written approval of the study and keep on file all IRB correspondence, including records of approval of all documents pertaining to this study. If the IRB imposes any additional requirements (e.g. safety reports, progress reports etc.), the Sponsor will prepare the required documents and send them to the Investigator for reporting to the IRB.

12.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, good clinical practices (GCP), and the applicable regulatory requirements.

12.3 Study participant Information and Consent

Prior to screening for the study, each study participant, as required, will be informed in detail about the nature of the clinical investigation with its expected risks and discomforts. The basic elements of informed consent as specified by the EU Directive 2001/20/EC will be followed. Written consent will be obtained from each study participant enrolled in the clinical study, as required, using the IRB -approved Informed Consent Form (ICF). The PI will verify the consent form. Each study participant will be given a copy of the Informed Consent Form. The study participants will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Prior to the start of the study, the PI will be provided with an actual stamped Informed Consent Form approved by the IRB for use during the study. At the conclusion of the study, the PI will provide a letter stating that a signed informed consent was obtained from each of the study participants. The signed informed consent forms will be kept on file in a secured, designated place at the study site for the required period of time.

13.0 STUDY ADMINISTRATION

13.1 Study Initiation

Prior to the start of this study, all pre-investigational requirements must be met by the PI and study site. Compliance will be confirmed by the study monitor during the pre-study visit. The pre-investigational requirements may include:

1. Current Curriculum Vitae and current medical licenses or medical numbers of the PI and all sub-investigators
2. IRB name and address; Department of Health and Human Services (DHHS) number, if applicable, or membership list
3. Written documentation of IRB approval of protocol (identified by protocol number and title) and informed consent document (identified by protocol number and title)
4. A copy of the IRB approved consent form
5. A signed Clinical Research Agreement.

13.2 Clinical Supplies

The PI will be responsible for the dispensing, inventory and accountability of all clinical supplies, exercising accepted medical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection by the Clinical Monitor upon request. Upon completion or termination of the study the PI will return all remaining clinical supplies to Neuronoff, Inc., or designee along with a copy of the inventory record and a record of the clinical supplies returned. Under no circumstances will the PI allow the investigational device to be used other than as directed by this protocol.

13.3 Case Report Forms (CRFs)

Neuronoff, Inc. will provide the CRFs. The PI will be responsible for the timeliness, completeness and accuracy of the information on the CRF. All entries must be legibly recorded in ink, with entry errors designated by a single-line cross out, initiated and dated, such that the original entry remains readable. If electronic records are used,

The PI will make these forms available for review and collection by the designated representative at each scheduled monitoring visit.

The PI will retain a file copy of each completed CRF. In addition, the PI will ensure that the monitor representative(s) have access to source documents (e.g., hospital and clinic records) to ensure accuracy and completeness of the CRFs during the periodic reviews.

13.4 Study Completion

Data and materials that are required before the study can be considered complete and/or terminated are:

- Laboratory findings, clinical data and all special test results from treatment through the end of the follow-up period
- CRFs (including correction forms) properly completed by appropriate study personnel and signed by the PI
- Completed Device Accountability Records
- Statement of outcome for each unanticipated adverse device effect reported
- Copies of protocol amendments and IRB approvals (if applicable)

13.5 Final Report

The purpose of this single center pilot study is to assess the safety and interface efficacy performance of the Neuronoff Basmati Insert. The results will be presented in a clinical report with the study data provided by the Primary Investigator (PI).

13.6 Retention of Study Records

The PI will retain copies of the approved protocol, completed CRFs, informed consent documents, relevant source documents, study-related correspondence and all other supporting documentation related to the project for the latter of a period of 2 years following the approval of a premarket application (U.S.) or 2 years from the time the study is terminated.

These files must be made available for inspection upon reasonable request by authorized representatives of the Ohio Pain Clinic.

13.7 Confidentiality

Study participant medical information obtained by the study is confidential, and disclosure to third parties other than those noted below is prohibited. We will follow HIPAA guidelines toward study participant information.

At the study participant's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection on request by representatives of Neuronoff, and the IRBs (if appropriate).

The information obtained in this study may be published in medical journals, but will not reveal the identity of the individual study participants.

13.8 Publication of Study Results

Results of this study will not be submitted for presentation or publication without the prior written permission of Neuronoff, Inc.

14.0 SIGNATURE of PRINCIPAL INVESTIGATOR

I have read the study protocol, entitled BASMATI - Basic Assessment of Safety and Minimally invAsive sTimulation via Injectrode. I agree to conduct the investigation in accordance with the agreement, the investigational plan and applicable EU and US regulations. Further, I agree to conduct the investigation in accordance with the conditions imposed by the reviewing IRB. This includes the supervision of the device involving human study participants and ensuring that the requirements for obtaining informed consent are met.

Printed name of Principal Investigator	Date
Signature of Principal Investigator	

15.0 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

1. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my study participant will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the study participant's interest when providing medical care which might have the effect of weakening the physical and mental condition of the study participant."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

2. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the

subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the study participant's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

3. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the study participants who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every study participant entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the study participant which aspects of the care are related to the research. The refusal of a study participant to participate in a study must never interfere with the study participant-physician relationship.

5. In the treatment of a study participant, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the study participant, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

16.0 REFERENCES, REGULATIONS AND STANDARDS

16.1 References

1. American Chronic Pain Association Resource Guide to Chronic Pain Medication and Treatment, 2014 Edition.
2. Trevathan JK, Baumgart I, Nicolai EN, et al. A Truly Injectable Neural Stimulation Electrode Made From an In-Body Curing Polymer/Metal Composite. BioRxiv. 2019 BioRxiv https://doi.org/10.1101/584995.
3. Deer TR, Levy RM, Rosenfeld EL. Prospective Clinical Study of a New Implantable Peripheral Nerve Stimulation Device to Treat Chronic Pain. Clin J Pain. 2010 Jun;26(5):359-72. https://doi.org/10.1097/AJP.0b013e3181d4d646
4. Deer TR, Pope JE, Kaplan M. A novel method of neurostimulation of the peripheral nervous system: The StimRouter implantable device. Tech Reg Anes Pain Manag. 2012 Apr;16(2):113-117. https://doi.org/10.1053/j.trap.2013.02.007
5. Deer T, Pope J, Benyamin R, Vallejo R, Friedman A, Caraway D, Staats P, Grigsby E, McRoberts WP, McJunkin T, Shubin R, Vahedifar P, Tavanaiepour D, Levy R, Kapural L, Medhail N. Prospective, Multicenter, Randomized, Double-Blinded, Partial Crossover Study to Assess the Safety and Efficacy of the Novel Neuromodulation System in the Treatment of Patients With Chronic Pain of Peripheral Nerve Origin. Neuromodulation. 2016 Jan;19(1):91-100: https://doi.org/10.1111/ner.12381
6. Acute Human Study: StimRouter for Peripheral Nerve Stimulation of Discrete Peripheral Nerves (SimRouter). First Posted April 23, 2008. https://clinicaltrials.gov/ct2/show/NCT00665132?id=NCT00665132+OR+NCT01592344&draw=2&rank=2&load=cart
7. Bioness® StimRouter™ Neuromodulation System for Chronic Pain Therapy. First Posted May 7, 2012. https://clinicaltrials.gov/ct2/show/NCT01592344?id=NCT00665132+OR+NCT01592344&draw=2&rank=1&load=cart
8. Geddes, L.A., Roeder, R. Criteria for the Selection of Materials for Implanted Electrodes. *Annals of Biomedical Engineering* **31**, 879–890 (2003). https://doi.org/10.1114/1.1581292
9. Hielm-Bjorkman A, Raekallio M, Kuusela E, Saarto E, Markkola A, Tulamo RM. Double-blind evaluation of implants of gold wire at acupuncture points in the dog as a treatment for osteoarthritis induced by hip dysplasia. *Vet Rec.* 2001;149(15):452-456. https://doi.org/10.1136/vr.149.15.452
10. Product: Soft Tissue Marker
    Composed of 99.95% Gold
    https://www.accessdata.fda.gov/cdrh_docs/pdf3/k031206.pdf
    https://www.accessdata.fda.gov/cdrh_docs/pdf9/K091645.pdf

11. Product: Gold Eyelid Weight Implants
    Composed of 99.99% Gold
    https://www.accessdata.fda.gov/cdrh_docs/pdf/K971242.pdf
    https://www.accessdata.fda.gov/cdrh_docs/pdf15/K150986.pdf

16.2 FDA guidance on Good Clinical Regulations for medical device studies

12. 21CFR820 Quality System Regulation
13. 21CFR50 Protection of Human Subjects
14. 21CFR54 Financial Disclosure by Clinical Investigators
15. 21CFR56 Institutional Review Boards
16. 21CFR812 Investigational Device Exemption
17. 21CFR814 Premarket Approval of Medical Devices
18. 21CFR822 Postmarket Surveillance
19. ICH Guideline on Good Clinical Practice
20. FDA Guidance on Investigator Responsibilities: Protection the Rights, Safety, and Welfare of Study Subjects.

16.3 ISO Standards

21. ISO 13485 Quality Management System
22. ISO 14971 Risk Management for medical devices

17.0 APPENDIX 1: Figures and Tables

17.1 Figures

17.2 Tables

18.0 APPENDIX 2: Included Documents & Components List

18.1 List of Included Documents

NDD-001	Injectrode Device Description
SOP-36-F1	Informed Consent Checklist
SOP-36-F2	Informed Consent Form
SOP-36-F3	Case Report Form
NCP-01-F4	Non-Significant Risk
NCP-01-WI-01	COVID-19 Mitigation Plan
REC-020	Histo-Pathology Report
SOP-02	Design Control Procedure
SOP-05	Risk Management Procedure
SOP-10	Investigator Selection Procedure
SOP-11	Clinical Site Initiation Procedure
SOP-32	Site Monitoring
SOP-33	Product Accountability
SOP-35	Site Closeout
SOP-36	Preparation of Informed Consent & Case Report Forms
SOP-34	Non-Significant Risk Studies
SOP-38	Adverse Events Reporting

18.2 List of Assembly and Component Parts

Final Assembly Part Number

Basmati Injectrode System Assembly: F-0001

Subcomponent Part Numbers

Cannula:	C-0001
Retaining Clip:	C-0002
Basmati Injectrode:	C-0003
Plunger:	C-0004