

Generic IRB Application for Research Involving the Electrodiagnostic sensory Nerve Conduction Threshold (sNCT) Evaluation

August 19, 2004

Diagnostic Transcutaneous Electrical Stimulation in Individuals

Purpose

A study will be conducted to evaluate an individual's sensory and/or pain perception response to the diagnostic application of non-invasive neuro-selective transcutaneous sinusoid waveform electrical stimulation. The measures obtained provide a quantitative index of an individual's nervous system functional integrity which will be correlated with their medical condition. The findings from this study will be used to characterize various disease conditions for basic research purposes and to aid in the standardization of the obtained measurements for routine clinical neuro-diagnostic purposes.

The fully automated quantitative neuro-diagnostic methodology for determining neuroselective sensory Nerve Conduction Threshold (sNCT) evaluation Current Perception Threshold (CPT) profiles provides unique measures of nervous system integrity. This method employs the non-invasive, non-aversive and painless application of transcutaneous electrical stimulation. The CPT measuring device has been in routine clinical use since receiving permission to market by the FDA in 1986. This device has been previously approved by various institutional review board committees for clinical studies since 1983 (Appendix A). A bibliography of recent publications is available from the internet (Appendix B). The same device can be used to measure a patient's Pain Tolerance Threshold (PTT). A PTT is the maximum amount of the atraumatic neuroselective electrical stimulus that a patient can tolerate.

Study Design

Both in and out-patients with sensory complaints will be selected by their physician for inclusion in this study. Standardized automated double blind CPT testing methodology will be performed upon each subject. In addition to CPT diagnostic methodology, PTT tests may also be performed. Clinical evaluation findings along with available pertinent findings from past records, including other diagnostic tests, will be considered in the assessment of each patient.

Data Analysis

Following completion of this study, patient data will be pooled for statistical analysis to assess the utility of the CPT evaluation for diagnostic purposes of the condition(s) being evaluated. Both parametric and non-parametric statistical analysis techniques will be applied for the evaluation of collected data. The evaluation of collected CPT data will follow the guidelines presented in the manufacturer's data evaluation

manual.

Subjects

Informed consent will be secured from each subject. Up to one hundred subjects will be selected by the investigator(s) for this study. Additionally, depending upon the clinical setting, up to one hundred healthy volunteer control subjects may be included in this study. The subjects will be tested over a 2 month period.

Initially, each subject's neurological history will be reviewed by an interview or an evaluation of available records. Additionally, each subject may receive a routine neurological examination with a special emphasis on sensory function. The administration of the current perception threshold evaluation will be based upon the clinical condition of each subject as determined by the investigator(s). Pertinent aspects of the subjects' history and clinical condition will be recorded.

Each subject's confidentiality is preserved by not using their names or other identifying characteristics in any paper, report, or presentation. Furthermore, all records will be kept in the Principal Investigator's office in a locked file except when being studied or updated. Patients can also withdraw from the study at any time, including obtaining their records if they so desire, without jeopardizing any other aspect of their treatment.

Inclusion / Exclusion Criteria: Both male and female subjects, ages 18 years and older, will be included in this study based upon availability. Criteria for inclusion will include clinical stability and ability to communicate the perception of a subjective sensation.

Methods of Recruiting: Subjects will be referred for this study by their physicians. Additionally, healthy volunteers (controls) will be recruited for this study by word of mouth. There will be no inducements for participation. Potential subjects expressing interest in participating will be given a description of the study. After the description, one of the investigators will discuss the study with the individual. Those continuing to show interest will be given a copy of the consent form. After reading the form, the individual will be asked if he/she has any questions concerning the study. After answering all of the questions, potential subjects will be asked to sign the consent form (Appendix D) if they wish to participate in the study. Subjects will be given a copy of the signed consent forms.

Benefits: Subjects participating in this study may benefit from the findings obtained through improved diagnosis of health conditions affecting sensory function. The results may also lead to improved methods for selecting treatments. Additionally, patients may benefit from the study through improved methods for monitoring the patient's response to treatment

Current Perception Threshold (CPT) Device

The NEUROMETER[®] CPT diagnostic stimulator to be employed for this study is manufactured by Neurotron Inc., 1501 Sulgrave Ave., Suite 203, Baltimore, Maryland 21209 U.S.A. It is portable and battery (6 V) operated device. NEUROMETER[®] CPT devices generate constant alternating current sinusoid waveform stimuli at 3 different calibrated frequencies: 2000 Hz, 250 Hz and 5 Hz. The range of stimulus output

intensities is from 0.01 to 9.99 mAmpères (mA). The constant current output enables highly reproducible measures which are unaffected by variables such as skin thickness, temperature or edema. The current is delivered to the skin surface via a pair of 1 cm diameter gold electrodes separated by 1.7 cm.

CPT Testing Methodology

Overview: The CPTs are obtained using a standardized testing methodology. Preferably, subjects are tested in a quiet examination room. During CPT testing, device controls are kept from the subjects view. Surface electrodes are placed over the skin at the body site to be tested. The subject is stimulated with three different sine wave frequencies (5 Hz, 250 Hz, and 2000 Hz) which increases in intensity (0-10 mA) until the subject experiences a painless sensation, characterized as a mild tingling, at or near the electrodes. The test is repeated to confirm the consistency of the response.

Detailed Description: The CPT test is administered at standardized cutaneous test sites that are specific for dermatomal and peripheral nerve evaluations. The entire test for each site requires approximately 3 to 5 minutes. Generally, body sites are tested bilaterally. The standardized CPT exam includes, preparing each test site with supplied prep paste, testing the subject at each body site with all three frequencies in the following order: 2000 Hz, 250 Hz and 5 Hz. A pair of gold electrodes is coated with a thin layer of conductive gel and then taped to the cutaneous site being tested. Next, an intensity alignment procedure is conducted to approximate the sensory threshold within a 50 μ Ampere range. Then, using an automated double-blind (microprocessor controlled) methodology, the subject is presented with 7-10 cycles of randomly selected real and false stimuli, above and below their perception threshold level, until the exact CPT value within that range is determined. This testing methodology is able to determine reproducible CPT measures within a \pm 20 μ Ampere range. See Appendix E for a sample script to be read to the subject explaining the CPT test.

Risks: There are no known major risks associated with the mild transcutaneous electrical stimulation that will be administered in this study. Every possible safety precaution has been used in the design of the battery powered stimulator to be employed in this study. Its output is via a 6 volt battery capable of generating a maximum constant alternating current of 10 mA. The only side effect is a brief slight reddening of the skin under the stimulation electrodes. This infrequent side effect typically disappears within 30 minutes. The potential hazards from the CPT evaluation are minimal. To date, approximately 7,000 NEUROMETER[®] CPT devices have been in routine clinical and research use worldwide with over 1 million CPT evaluations performed and no adverse complications reported.

PTT Testing Methodology

Overview: The PTTs are also obtained using a standardized methodology. The same device and electrode assembly that is used for the CPT test is used for the PTT test. The subject will be stimulated with three different sine wave frequencies (5 Hz, 250 Hz, and 2000 Hz) with a constant alternating current which increases in intensity (0-10 mA) in an automated staircase presentation until the sensation becomes to painful to tolerate. The subject controls the stimulus intensity and can discontinue the

test at any time by releasing the button on the Remote Box. The test is performed, initially, on a body site not involved in the study to familiarize the patient with the procedure.

Detailed Description: The entire test for each site requires approximately 2 minutes. First, the gold electrodes are coated with a thin layer of conductive gel are then taped to the test site. Next, the subject is told that this test is conducted with 3 different types (frequencies) of electrical stimuli - each of which produce a slightly different sensation. Although the sensations may include tingling, vibration, pressure or burning, there is no actual vibration, pressure or burning of the tissue occurring. The subject assured that the stimulus is completely safe and that any pain experienced is a transient phenomenon that will only last a brief instant.

The subject is next given the CPT/C Remote Box which has a series of buttons on the top. The subject is told that pressing and holding a Remote Box button will cause an increasingly intense stimulus to be emitted through the electrodes. The subject is instructed to press and hold the button until the stimulus is initially perceived, then to continue to press and hold the button as the stimulus continues to become more intense. Continue to press and hold the button until the stimulus becomes painful - and only release the button when the pain becomes intolerable. As soon as the button is released, the stimulus ceases. The subject should also be informed that it is possible that the stimulus may become increasingly intense without becoming painful. In that event, the stimulus will automatically stop at a predetermined level. When the Remote Box button is released or the stimulus automatically shuts off, the CPT/C device will record the corresponding PTT level.

Initially, on a body site not involved in the study, the test should be repeated at the same frequency for as many times as necessary for subject familiarization with supra-threshold sensations and pain sensations that may be evoked by the electrical stimulus. Actual PTT testing will be conducted once and should begin first using the 2000 Hz stimulus, and then proceed using the 250 Hz and finally the 5 Hz stimulus. A one minute rest period should be allowed between each PTT determination. See Appendix F for a sample script to be read to the subject explaining the PTT test.

Risks: The chance of adverse effects on the subject is minimal since sNCT evaluation CPT and/or PTT measurements are non-invasive. The use of this equipment may, however, make some of the subjects agitated. The subjects will be managed by the principal investigator and if necessary, the measurement of CPT and/or PTT will be terminated.

Appendix A. Prior Studies

Review board committee approval for previous clinical studies using the CPT device have been obtained at numerous institutions including the following:

City University of New York
Creighton University School of Medicine
Johns Hopkins Medical Institution
New York Medical College
University of California School of Medicine, Los Angeles
University of California School of Medicine, San Diego
University of Kansas School of Medicine
University of Miami School of Medicine
University of Texas School of Medicine, Houston
University of New Mexico School of Medicine
Virginia Mason Clinic
Vanderbilt University
Stanford University
Texas Tech University
Cleveland Clinic Foundation
Cook County Hospital

Appendix B. Comprehensive Bibliography of Automated Electrodiagnostic Neuroselective sNCT Evaluation with Current Perception Threshold (CPT) Measures Publications is available from the Internet at: <http://www.neurotron.com/abstracts/index.html>. The following is a general review article:

Katims, J.J. Electrodiagnostic Functional Sensory Evaluation of the Patient with Pain: A Review of the Neuroselective Current Perception Threshold (CPT) and Pain Tolerance Threshold (PTT). Pain Digest Volume 8(5), 219-230, 1998.

Appendix C.

Title of Study: Diagnostic Transcutaneous Electrical Stimulation in Individuals

Brief Summary of Proposal

This study will use Current Perception Threshold (CPT) measurements from both healthy subjects and patients using non-invasive and non-aversive neuro-selective transcutaneous electrical stimulation. Additionally, Pain Tolerance Threshold (PTT) measures may be obtained. The measures obtained provide a quantitative index of an individual's nervous system integrity that will be correlated with their medical condition. The findings from this study will be used to characterize various disease conditions for basic research purposes as well as to allow the standardization of the obtained measurements for routine clinical neuro-diagnostic purposes. The subject population will consist of up to one hundred normal individuals and up to one hundred pathological individuals, both male and female, at least 8 years of age. The study will require up to two months for completion. The study is expected to increase knowledge of the sensitivity of the CPT and PTT evaluation in its ability to characterize different

pathological/physiological conditions. This information may then be used for the study of various associated pathological/physiological conditions affecting the nervous system and assist in the therapeutic management of the patient.

Appendix D.

Title of Study: Transcutaneous Electrical Stimulation in Individuals

Consent To Participate in a Clinical Research Study

RESEARCH TITLE: **Comparison of sensory perception threshold values in patients and healthy subjects**

PRINCIPAL INVESTIGATOR :

SITE OF INVESTIGATION:

I am being asked to be part of a clinical research project. Before I decide that I will be part of the study, I am asked to read this information and ask as many questions as I want about the study. I will not agree to be in the study unless I fully understand what will happen and until I freely decide to be part of it. I understand that I have the right to refuse to answer any question that I may not wish to answer.

I understand that I will not be excluded from this study based on language considerations. Translation will be provided if I request.

PURPOSE OF THE STUDY

(Patients)

The purpose of this study is to evaluate both sensory perception and pain perception in the effected toe or finger or body site where I have pain as well as in a finger or toe where I do not have any pain. The evaluation will be conducted using an electronic sensory Nerve Conduction Threshold (sNCT) test.

(Healthy Volunteers)

The purpose of this study is to determine the healthy relationship between sensory perception and pain perception thresholds in my finger and toe or another body site. The evaluation will be conducted using an electronic sensory Nerve Conduction Threshold (sNCT).

(All)

We are asking you to participate in this research project in which sensory perception threshold measurements will be taken from both healthy and diseased individuals. The purpose of this study is to further knowledge of the nervous system. The measures obtained provide a quantitative index of an individual's nervous system integrity that will be correlated with their medical condition. The study is expected to increase knowledge of the utility of this evaluation in its ability to characterize different pathological conditions. This research study evaluates nerve function. Nerves will be tested for sensation and pain thresholds. The study is non-invasive and will not use

needles. The equipment being used has been in routine clinical use since 1986. A controlled electrical stimulus will be applied to the skin. The stimulus is specific to certain nerves that convey sensations such as touch, vibration, pressure, temperature and pain. The stimulus will not injure the skin.

For the evaluations, small electrodes will be placed on my fingers and then my toes. The quantitative sensory testing device sends out small electrical signals. I will be asked by the tester to indicate whether or not I can feel slight, non-painful tingling or pain sensations at or near the site of the electrodes. This entire sensory testing procedure will last 15 to 25 minutes.

PROCEDURES TO BE PERFORMED DURING THE STUDY

I understand that this measuring sNCT device is a portable battery-operated machine which will stimulate the nerves.

I will be scheduled for measurement of threshold values by this machine at one time only. With the electrodes placed at the selected site or on a finger and/or a toe, the current will be increased gradually until I feel the onset of tingling, buzzing or warmth at the sites of the electrodes. The current will be decreased gradually until there will be no sensation of stimulation. The procedure will then be repeated where I hold the test button to increase the stimulus intensity above my sensory threshold until the device automatically shuts off or until I release the test button to stop the test in the event that electrical stimulus becomes too painful to tolerate. It is **not** necessary that I experience pain in order for the sNCT device to automatically shut off.

POTENTIAL RISKS

The adverse effect of the electrical sensory Nerve Conduction Threshold (sNCT) measurement is minimal because the procedure is non-invasive. In the 18 years that the sNCT device has been employed there have never been any serious adverse reactions reported. The use of this device may make me uncomfortable. If that occurs I am assured that I will be taken care of by the principal investigator and if I request, the testing stopped.

The electrode paste used in this study is hypo-allergenic and water soluble. Although it is unlikely, there is a chance that a slight reddening of the skin may occur under the electrodes. If so, this will disappear within 30 minutes.

POTENTIAL BENEFITS OF THE STUDY

The data obtained from the study will benefit future patients who suffer from certain types of pain conditions. It is believed that the findings will benefit patients in the future by enabling them to be diagnosed and treated earlier. I may not get the benefit from this study directly.

I understand that I can, at any time during the study, withdraw from the study

without penalty or loss of benefits to which I am otherwise entitled.

NOTIFICATION OF FINDINGS

If any new information is discovered which may effect my participation in this study, I will be notified of it.

WITHDRAWAL FROM THE STUDY

My participation in this study is purely voluntary, and I may withdraw my permission and discontinue my participation at any time without penalty. My treatment and the care given to me by my doctors and nurses will not suffer as the result of my withdrawal. Should I wish to withdraw my consent, or if I have any questions about the investigation, my rights as a research subject, or if I need to report any research related injury(s) I will notify the investigator or one of the study personnel. The names and phone numbers of the people to contact are listed here:

I understand that if I have any questions, comments or concerns about the study or the informed consent process, I may write or call the office of the Research Programs.

My participation in the study may be discontinued at any time without my consent by my doctor or the U.S. Food and Drug Administration (FDA). If I fail to comply with study procedures, my participation in the study may be discontinued.

RELEASE OF MEDICAL RECORDS AND CONFIDENTIALITY

The medical record identifying you will be maintained by the principal investigator or co-principal investigators. Your identity will remain confidential if material from the record is used for publication or for educational purposes. Only group results will be reported. However, you should be aware that there is a possibility that the Food and Drug administration may inspect the records under regulatory law.

By signing this consent form, I agree that the FDA and perhaps other regulatory

agencies may inspect and copy my medical records relating to the study. The people who receive this information will treat as confidential.

Consent To Participate in a Clinical Research Study, continued

CONSENT

This consent form contains important facts so that I or my legal representative can decide if it is in my best interests to participate in this study. If I have any questions that are not answered in this consent form, one of the researchers will be available to give me further information.

Before giving consent by signing this form, I or my legal representative have had an opportunity to ask questions about the research study described in this consent form. Based on this information, I voluntarily agree to participate in the study. All oral and written information and discussions about the study are in a language in which I or my legal representative are fluent.

Signature of Subject or Legal Representative

Date

Printed Name of Subject or Legal Representative

Signature of Witness

Date

Printed Name of Witness

INVESTIGATOR'S STATEMENT

I, the undersigned, certify that to the best of my knowledge, the subject/participant signing this informed consent has had the study fully and carefully explained and clearly understands the nature, risks, and benefits of participating in this research project.

Signature of Investigator

Date

Printed Name of Investigator

Appendix E: Sample Subject Script for the CPT Test

After Pre-Exam Cable Test / Before CPT Test

"This device gives a very low level of electrical stimulus through a pair of small gold electrodes taped to your skin. This test is painless. First, I'll attach the electrodes to you. Then, I'll slowly increase the intensity of the stimulus until you tell me that you can feel it. You may feel the stimulus beneath or around, or even beyond the electrodes. If at any time it hurts, tell me, and I'll turn it off immediately. I'll repeat this procedure several times."

After Intensity Alignment / Before CPT Testing Cycle

"Next, I'll perform a series of test cycles. During each cycle, there will be two tests, Test 'A', a rest period and then a Test 'B' as indicated by these lights. (Point to the corresponding lights on the Remote Box). After Test 'B' all three lights will come on. If you felt Test 'A' stronger push the Test 'A' button, if you felt Test 'B' stronger push the Test 'B' button. If they both felt the same or if you felt neither one push the 'Rest/None' button. Push the red 'Test Cycle' button to continue the test." The test will end automatically."

Before CPT Testing at Different Frequencies

"Now we'll repeat the same procedure testing a different sensation. It may produce a slightly different sensation. Once again, tell me when you feel a sensation at the electrodes."

Appendix F: Sample Subject Script for PTT Test

Pain Tolerance Threshold (PTT) Determination

"Begin the test by pressing and holding the red TEST CYCLE button on the remote box. As you hold it, the stimulus will gradually increase and you'll feel it getting stronger and stronger. You need to keep holding the button for as long as you can – until it becomes too painful to tolerate. As soon as you let go, the stimulus will immediately shut off. Please keep in mind that it's very important to hold the button down for as long as you can. For some tests, the stimulus may produce an intense tingling sensation but may never become truly painful. In those situations, it's important to try to hold down the button until the stimulus automatically shuts off. Again please note that you cannot be injured by this stimulus."

(Following the PTT Determination)

"Please tell me if the stimulus was clearly painful or was it just so intense that you had to let it go?"

Now, we will repeat the test. It may feel slightly different, once again just hold the "TEST CYCLE" button until the stimulus becomes clearly painful."