Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

You are invited to participate in an investigational research study of the efficacy of Low-Dose Naltrexone (LDN) at 4.5 mg dosage in relieving symptoms of Complex Regional Pain Syndrome (CRPS). The medication used in this study is FDA approved for the treatment of alcohol and drug abuse at 50 mg dosage but not for the treatment of CRPS at 4.5 mg dosage. We hope to learn several things from this study:

- We want to see if LDN can be used to treat CRPS.
- We hope to better understand the complex relationship between the different CRPS symptoms.
- Some people respond better than others to LDN and we wish to find why.

You were selected as a possible participant in this study because you are currently diagnosed with CRPS.

If you decide to terminate your participation in this study, you should notify the Research Coordinator, Birute Gedrimaite, at birute@stanford.edu or (650) 497-0485.

This research study is looking for 120 participants with CRPS, all to be recruited at Stanford University.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

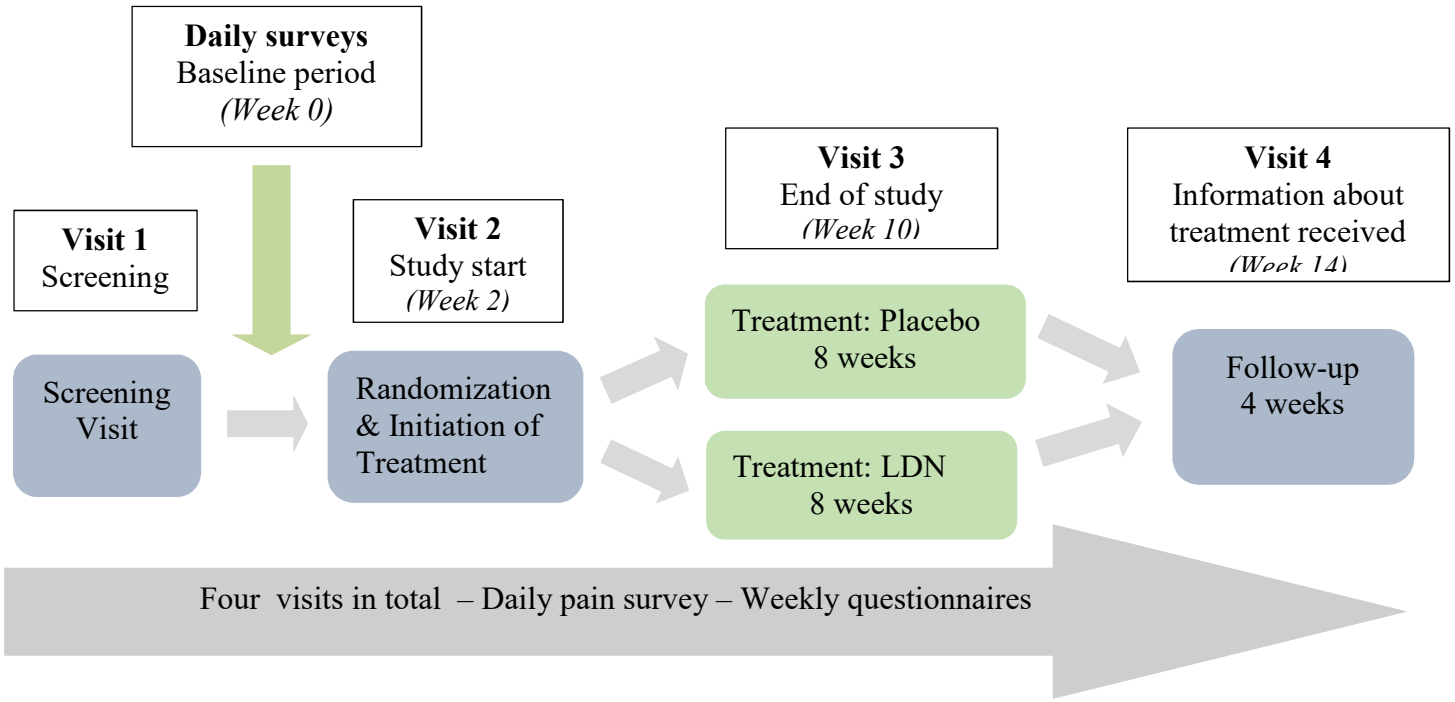
This research study is expected to take approximately 10-15 years. Your active participation is expected to take up to 14 weeks including 2 weeks of baseline information gathering, 8 weeks of drug treatment, and 4 weeks of follow up.

At the end of this period, you may be offered the opportunity to receive LDN and participate in electronic surveys for an additional 14 weeks. You may also be asked to fill

out an electronic survey at 6 months and 12 months after active participation in this study.

PROCEDURES

If you choose to participate, the Protocol Director and his research study staff will ask you to take part in the following:



** If you were in the placebo arm, you may have the opportunity of continuing with the research study to receive LDN at no cost for an additional 8 weeks.*

1. <u>Baseline/Screening Visit:</u>

The first step is to confirm your eligibility with the research team. This is to make sure you are a good fit for the study. You may be asked to complete detailed questionnaires about your demographic information, medical history, medications and treatment, mood, personality, and pain information. This visit may take 1-2 hours and may include the following:

Physical Exam & Assessment – You may have a brief physical exam and physical assessment with the research team. This is to better characterize your pain, symptoms, balance, strength, and range of motion. We may also record your height, weight, blood pressure, heart rate, and other vital signs, and measure your

affected and unaffected limbs' circumference, volume, and temperature. Volume may be measured by placing your limbs in a tank of water.

Limb Capture – We may take pictures of your limbs to document color and size. These pictures will only be identified by your study ID number and may not be used to identify you.

CSS Evaluation: Sensory, Vasomotor, Sudomotor, Motor/ Trophic Changes. Pressure QST, IR Thermometer, Dynamometer, 2 Minute Walk. – Where a checkbox is present, you may participate in the tasks that are checked off by a member of the research team and by which you initial.

Before, during, or after testing you may be asked to respond to questions and rate your pain experience. Testing may be repeated several times in one session. Before any testing occurs, a member of the research team will carefully review each procedure with you and answer any questions that you may have.

_____ ☐ 1. *CSS Evaluation:*

1.1. Sensory:

_____ ☐ a. Allodynia
_____ ☐ Light touch
_____ ☐ Cold
_____ ☐ Heat

_____ ☐ b. Hyperalgesia to Pinprick
_____ ☐ Hypoesthesia

_____ ☐ c. Pain when Moving the Nearest Joint

1.2. Vasomotor:

_____ ☐ a. Color Asymmetry
_____ ☐ b. Temperature Asymmetry by Palpation

1.3. Sudomotor:

_____ ☐ a. Sweating Asymmetry
_____ ☐ b. Edema Asymmetry (Swelling)

1.4. Motor/Trophic Changes:

_____ ☐ a. Dystrophic Changes
_____ ☐ b. Motor Abnormalities
_____ ☐ c. Decreased ROM

_____ ☐ 2. *Pressure QST*

_____ ☐ 3. IR Thermometer

_____ ☐ 4. Dynamometer

_____ ☐ 5. 2 Minute Walk Test

Blood Sampling – We may ask you for a fasting blood draw, which will take approximately 15-40 minutes. If we ask you for a blood draw, we would like you to participate in our separate blood draw study and read the Research Information Sheet for "Biological Predictors of the Pain Experience" which outlines the procedures for blood sampling and genetic testing for research.

_____ ▪ Phlebotomy and biobanking: Information sheet "Biological Predictors of the Pain Experience" read and understood, agree to give blood sample within this study.

_____ ▪ Agree to give a blood sample in this study.

_____ ▪ **Do not** agree to give a blood sample in this study.

We may also ask you to start completing a 10-minute questionnaire, which may be administered to you once a week for the duration of your participation. In addition, we may ask you to complete a daily pain score every day for the duration of your participation.

We may also supply you with an actigraphy unit and ask you to wear it during your participation. We may use the information the actigraphy unit collects to assess your activity and rest/sleep cycles. You will be asked to return the unit at the end of your study participation.

By the end of this visit, if you are found eligible, you will be asked to complete the 2 week baseline period (detailed below) and scheduled for treatment initiation visit where you may be randomly assigned to one of the two treatment groups as will be described below. This is like flipping a coin to decide whether you will receive LDN or placebo.

2. 2-Week Baseline Period:
Following your screening visit, we may ask you to complete the daily survey and weekly questionnaire.

3. Treatment period

At the end of the 2-week baseline period, we may ask you to come to the lab to be randomized into one of the two treatment groups and to begin taking the medication, once a day at bedtime, for this entire period. You will be provided with a supply of either LDN or placebo (an inactive sugar pill), depending on which group you were randomly assigned to. Neither you nor the research team will know to which group you were assigned.

We may ask you to come to the lab at the end of treatment, and this visit may include the following:

- A brief physical exam/assessment similar to the one described in the baseline visit
- Sensory testing as described for the baseline visit
- Blood sampling as described for the baseline visit

4. Follow-Up Period:

During these 4 weeks you will not be taking medication. We may ask you to continue with the daily and weekly questionnaires, and come in for lab a visit the last week (Week 14). At this final visit, we may tell you if you were on the LDN or the placebo group. If you were on the placebo group, you may have the opportunity of continuing in the research study for 14 additional weeks with 8 weeks of LDN at no cost. During these 14 weeks, you will not be required to come in for visits. In order to secure this extended LDN period, we may ask you to continue to answer the weekly questionnaires and daily pain scores, and we may also call you once every two weeks to ask how you are doing. You may also be asked to complete an electronic survey at 6 and 12 months after active participation in the study.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper

use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Take the study drug as instructed.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Keep the study drug in a safe place, away from children and for your use only.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Birute Gedrimaite at 650-497-0485. Alternatively, you may send her an email at birute@stanford.edu. If possible, please let us know why you are deciding to withdraw. You may also notify the Protocol Director, Sean Mackey, MD, PhD, at (650) 725-9636.

If you withdraw from the study, or the study medication is stopped for any reason, you must return all study related supplies, including unused study drug.

The Protocol Director may also withdraw you from the study and the study medication may be stopped, without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.

- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

LDN:
Some participants report mild insomnia in the first few days of taking LDN.
At 4.5 mg, side-effects of LDN are expected to be considerably less than at the standard naltrexone dose of 50mg. Naltrexone at it full strength is known to produce side-effects in individuals with an opioid or alcohol addiction, but not in healthy controls. Side-effects associated with the full dose of 50mg include: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%), and somnolence (2%). Your daily dose of naltrexone will never exceed 4.5mg.

Tactile Stimulation:
Pressure applied using a pressure plunger or algometer may cause temporary pain, tenderness, discomfort, and/or bruising to the area where pressure is applied. You will be able to stop the test at any time if the pain becomes too intense. The researcher conducting the test will remove the pressure being applied if you find it too discomforting.

The pressure test may cause some temporary tenderness, pain, and/or bruising where pressure is applied. You will be able to stop all pressure testing at any time if the pain ever becomes too intense to tolerate.

Discontinuing Medication
There is a risk that discontinuing LDN during the washout period of this study may result in reoccurrence of signs and symptoms of CRPS.

Additional risks:

There is a risk you may feel uncomfortable answering some of the questions on the questionnaires. You have the right to refuse to answer particular questions

It is possible that, based on information gained from this study, the investigators may be required to report information (e.g., information relating to suicide, physical or sexual abuse) to the appropriate authorities.

The testing, as with any testing, may be an inconvenience or uncomfortable, but the tests are not known to cause undue distress. These procedures may involve risks to the subject which are currently unforeseeable.

There risks from the blood draw include bleeding, soreness, bruising and stinging at the site of the blood draw.

POTENTIAL BENEFITS

We cannot and do not guarantee or promise that you will receive any benefits from this study. However, you may experience relief from your CRPS symptoms due to the medication.

ALTERNATIVES

At this time, there is no consensus on effective treatment for CRPS. Some physicians may prescribe off-label LDN as part of your clinical care, and you should discuss this with your physician as an alternative to participating in the study. If a new treatment emerges during your participation in this study, you will be informed of the alternative. The alternative to this study is not to participate.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell either Birute Gedrimaite or the Protocol Director, Sean Mackey, MD, PhD.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify

you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

The purpose of this research study is to obtain data or information on the safety and effectiveness of low-dose naltrexone; the results will be provided to the Food and Drug Administration and other federal and regulatory agencies as required.

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

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

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The main purpose of this study is to learn whether the medication LDN can be effective in treating CRPS. Your individual health information will be used to learn more about this question, as well as to identify the relationship between the various CRPS symptoms and predictors of who might have a stronger response to LDN. Our results and conclusions will be submitted for publication, but no identifying information about you will be published. We may also provide results to the FDA.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your

health information in this study, you must write to: Sean Mackey, MD, PhD at 1070 Arastradero Road, Suite 200, Palo Alto, CA 94304.

What Personal Information Will Be Obtained, Used or Disclosed?
Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, your name and contact information, basic demographic information, your medical and medication history, the information you provide on the questionnaires, results of your physical exam & assessment, actigraphy data, and sensory testing results.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director Sean Mackey, MD, PhD
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The Food and Drug Administration

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on December 31, 2060 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment
Where a checkbox is present, you will be reimbursed that are checked off by a member of the research team and by which you initial.

You will receive:
_____ ☐ $30 per in – person visit, for a total of up to 4 visits or $120.
_____ ☐ $25 as payment for giving a blood sample, for a total of up to 2 blood draws or $50.

Should you complete the study and attend all visits, you will also receive a $100 bonus payment following your final follow-up visit.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Costs
There is no cost to you for participating in this study, other than basic expenses like transportation and the personal time it will take to come to all of the study visits.

The study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. If you would like to review the list of such covered services, supplies, procedures and care, please tell us now or at any time during the study. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance**. Participation in this study is not a substitute for health insurance.

Sponsor
This study is being funded by a gift donated by The Reflex Sympathetic Dystrophy Syndrome Association (RSDSA)

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be**

responsible for any associated co-payments or deductibles as required by your insurance.

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Appointment/Alternate contact: If you need to reschedule your appointment or if you cannot reach the Protocol Director, please contact Birute Gedrimaite at 650-497-0485.

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Sean Mackey, MD, PhD, at (650) 725-9636. You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;

- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you? ☐ Yes ☐ No

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent