UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Closed-Loop Deep Brain Stimulation for Refractory Chronic Pain Using Summit RC+S

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This is a clinical research study. Your study doctors, Edward Chang MD, from the UCSF Department of Neurological Surgery or Prasad Shirvalkar, MD, PhD, from the UCSF Department of Anesthesiology and Neurology will explain this study to you.

STUDY SUMMARY

Introduction: We are asking you to consider taking part in a medical research study being done at UCSF. Medical researchers are exploring an option for treating your chronic pain involving brain surgery. This type of surgery is done with deep brain stimulation (DBS), which involves delivering small electrical stimulation to areas in the brain that might alter the pain you're experiencing. The devices used in this study are investigational, which means they are *not* approved by the Food and Drug Administration (FDA) to treat chronic pain.

The first part of this consent form gives you a summary of this study. We will give you more details about the study later in this form. The study team will also explain the study to you and answer any questions you have.

Research studies include only people who choose to take part. It is your choice whether or not you want to take part in this study. Please take your time to make a decision about participating. You can discuss your decision with your family, friends and health care team.

Study Procedures: If you choose to be in this study, there will be multiple stages.

- **Stage 0:** This stage involves surgically implanting electrodes into multiple pain-related regions of the brain. You will stay in the hospital for up to 10 days. If you already have a deep brain stimulation device implanted and are enrolling into the study to utilize the rechargeable DBS system, you will not participate in this stage. Participation in the

Stage 0 trial does NOT guarantee inclusion into the whole study, and it is possible that you will not continue to Stage 1. You will still require another surgery to remove the temporary electrodes.

- **Stage 1:** This stage will last up to 6 months. If you completed Stage 0, we will remove the temporary electrodes, implant additional electrodes and connect it to the Summit RC+S. It is expected you will recover in the hospital for approximately 2-3 days, perform brain recordings at home, and come in for visits. If you already have a pre-existing DBS implant, you will undergo a procedure to remove and disconnect your current DBS implant from your implanted leads, and subsequently implant the Summit RC+S system in the same location in the upper chest and reconnect it to the leads already in place. The goal of Stage 1 is to discover a brain signal related to pain that may respond to stimulation.
- **Stage 2:** This stage will last up to 6 months. We will stimulate the brain, both in the clinic and at-home. At the beginning of Stage 2, you will have to come to the clinic every day for up to 2 weeks.
- **Stage 3**: This stage will last up to a year. We will set the brain stimulation settings to be always active in an at-home setting, and have you come to the clinic every 4-6 weeks, to check on your pain and possible pain relief. During this time, we will do additional testing in the clinic and may adjust stimulation settings.
- **Long-Term Follow-Up:** After the study is finished and if it is possible to leave the device on, you will come back for follow-up appointments every 6-8 weeks.

Possible Risks: There are risks to taking part in a research study. Some of the most likely risks of participation in this study include:

- Risks and side effects related to DBS surgery, which can range from likely risks of temporary pain/headache to less likely risks of bleeding inside the brain that could cause paralysis, coma, or death.
- Risks and side effects related to implanted DBS electrodes which include not being able to get MRIs while the electrodes are implanted.

Possible Benefits: There will be no direct benefit to you from participating in this study, although one of the goals of the study is to provide chronic pain relief.

Your Other Options: You do not have to participate in this study. Your other choices may include:

- Getting standard pain treatment without being in a study.
- Using other pain treatment alternatives such as different classes of pain medications, spinal injections, spinal cord stimulation and/or drug pump medical devices.

Please talk to your doctor about your choices before agreeing to participate in this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the study. If you join this study, we will give you a signed copy of this form to keep for future reference.

DETAILED STUDY INFORMATION

This part of the consent form gives you more detailed information about what the study involves.

Research studies include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because your current and/or other treatment options have not adequately treated your chronic pain.

The surgery devices in this study for pain are investigational, which means they are *not* approved by the Food and Drug Administration.

This study will measure activity in areas of your brain known to be involved in pain when you report being in pain and not in pain. The study will also investigate if stimulation of these areas can change your pain symptoms. The main goal is to develop a personalized program of brain stimulation for you based on your unique brain signatures of pain, also known as "Closed-Loop Brain Stimulation", to see if there may be any effects of brain stimulation on your chronic pain.

Who is paying for the study?

This study is funded by the National Institute of Health and the National Institute of Neurological Disorders and Stroke. The implantable devices used are provided by Medtronic, Inc. for research purposes.

Drs. Chang or Shirvalkar will not be receiving money from Medtronic Inc. during the course of this study. These disclosures are being made so that you can decide if this relationship will affect your willingness to participate in this study.

What are the costs of taking part in this study?

The costs of all clinical visits, treatments, and tests described above will be billed to you or your insurance carrier, with the exception of all implant devices and related materials (leads, electrodes, generators etc.), which will be provided by Medtronic. Insurance companies and other carriers sometimes refuse to pay the costs of treatment when individuals are participating in research. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay.

Due to the nature of this study, we will not proceed with the surgery and any clinical procedures if your insurer does not approve coverage of the care. All procedures done only for research will not be charged to you or your insurer. Financial counselors are available through the hospital accounting department to discuss what your insurance carrier will and will not cover. You do not have to continue with the study (i.e. Undergo physical examination, brain scans or the surgery portion and the other phases of the study) until you know and have indication of coverage from your insurance on the specifics of what will and what will not be covered.

How many people will take part in this study?

About 5 people will take part in this study at UCSF.

What will happen if I take part in this research study?

This study consists of a Baseline (Screening) period, a brain stimulation trial period (stage 0) and 3 stages of testing.

Stage 0: Brain stimulation trial period in hospital (up to 10 days)
Stage 1: Chronic device implant and measuring brain activity (up to 6 months)
Stage 2: Stimulation testing and recording (up to 6 months)
Stage 3: Comparing personalized stimulation to standard stimulation (1 year)
Long-Term Follow-Up

Depending on your results from stage 0, you might not be eligible to proceed to all 3 stages.

You will continue your current chronic pain treatment (psychotherapy and/or medication/injections) throughout the study.

Before You Begin

Prior to the start of the study, we will describe the study to you on the phone briefly and then schedule an **outpatient pre-surgery visit or visits (Figure 1)** where we will describe the study in detail and answer all of your questions. We will also have you fill out questionnaires that ask you about your mood, general health, memory functioning and pain states.

The research team may consult with your regular pain treatment team during the time. Prior to surgery, there will also be a physical exam to measure your pain condition and symptoms. If you agree to participate, you will be asked to sign a consent form agreeing to testing including medical screening, an evaluation of your neurological abilities, medical and psychiatric history, videotaping, brain scans, phone communication and surgery.

If the researchers determine you are eligible to continue the screening process, up to 5 other appointments will be necessary prior to the first surgery (there are 2 surgeries involved with this trial). These include:

- Appointment with your primary care provider to ensure it is safe for you to have brain surgery and participate in this study.
- Appointment with a psychiatrist for neuropsychiatric evaluation
- Pre-surgery appointment with the anesthesiologist
- Pre-surgery appointment with the neurosurgeon
- MRI scan to take pictures of your brain which will allow us to plan for brain surgery. For the MRI exam, you will lie down on a narrow bed that will then be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will need to lie there quietly

for about 1-2 hours, during which time there will be a loud banging noise. You may feel warm during this procedure and you will have multiple scans in this session. MRIs use magnetic fields and radio waves to produce their images. The MRI will be performed by the UCSF Radiology team located at the UC Imaging Center at 11 Irving Street or at Moffitt Hospital at the UCSF Parnassus campus.

***If you enroll in the main part of the study and have the DBS device implanted, you cannot have another MRI while the device is in your body. This device is not MRI safe.**

You will be required to have a caregiver who will participate in the study with you, by attending clinic visits and completing questionnaires. We will ask you to consent to be videotaped for portions of this study.

STAGE 0: Brain stimulation trial period in hospital (up to 10 days)

(This stage is optional and may not be performed. If you already have a deep brain stimulation device implanted and are enrolling into the study to utilize the rechargeable DBS system, you will not undergo the stimulation trial period (stage 0).)

What can you expect?

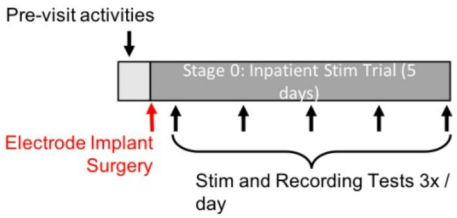

Figure 1

Stage 0 begins with the first surgery and requires you to undergo up to a 10-day trial period in the hospital in which electrodes are implanted in multiple pain-related regions of the brain. This will involve surgically implanting small, thin, wire-like devices called electrodes in both sides of your brain in regions that regulate your pain. Then, your response to stimulation is tested. The researchers will test stimulation in different brain regions. We will also record your natural brain activity. Because everyone's brain is different, researchers will try to learn more about how *your* brain communicates and how it may be responding abnormally to produce *your* specific type of pain.

It could take several months to get an appointment for the stage 0 surgery, so during this time you will complete your pre-surgery appointments.

Electrode Trial Surgery (Surgery 1 of 2)

The thin wire electrodes record brain activity in the brain areas that they are placed. The electrodes can also deliver small pulses of electrical stimulation.

The surgeon will place the electrodes through small holes drilled into the skull (burr holes). The

electrodes may also be placed in or on regions of the brain by temporarily removing the bone flap in the skull to better access the brain (craniotomy). Then, the electrodes will be secured to your skull and exit your scalp safely under bandages, so they can be accessed later. The electrodes used in this study are FDA-approved for the monitoring of brain activity and are commonly used in surgery for epilepsy.

In this study, different regions in the brain related to pain are being studied. The regions implanted will be done in consultation with the surgeon and pain treatment team. These areas may vary across patients who participate in the study.

Depending on your pain symptoms, you may have one side or both sides of the brain implanted with up to 5 wire electrodes for a maximum total of 10 wire electrodes for the 10-day trial period. After surgery is completed, you will remain in a part of the hospital out-patient unit where patients who have had brain surgery are typically monitored (neurosurgical transitional care unit (NTCU), epilepsy monitoring unit (EMU)) in the hospital for 1 day, unless a longer stay is deemed necessary by the treatment team.

You will then either be discharged to the Interventional Psychiatry Laboratory at LPPI at the Parnassus campus or remain in the hospital where you will stay for up to 10 total days under the care of a licensed physician and nursing staff. During this time, your chronic pain symptoms will be closely monitored and evaluated, and your brain activity will be recorded continuously. The researchers will be stimulating and recording different areas of your brain to look for your unique pattern of brain activity which may correspond to your chronic pain symptoms. We will be stimulating your brain and asking you questions at least 3 times per day. We will also be asking you to complete tasks related to your pain or memory. Task details are described in the section: *Stage 1- Out-patient appointments (Months 1-6).* You will be staying overnight, but you will have opportunities throughout the day to come and go for brief periods (outside of meeting with your study team) accompanied by a nurse and/or caregiver depending on the discretion of the physician. You will have access to a television and shower (you will need to follow the bathing instructions given by the neurosurgeon). You may go for walks outside, but we ask that you remain on the UCSF Parnassus campus.

If the researchers determine that there is a part of your brain that responds to stimulation and improves your symptoms, you may be offered the possibility to continue to the next stage (stage 1). Otherwise, the electrodes will be removed in another surgery and the trial will end.

Participation in the Stage 0 trial does NOT guarantee inclusion into the whole study, and it is possible that you will not continue to Stage 1. You will still require another surgery to remove the temporary electrodes.

STAGE 1: Chronic device implant and measuring brain activity (up to 6 months)

What can you expect?

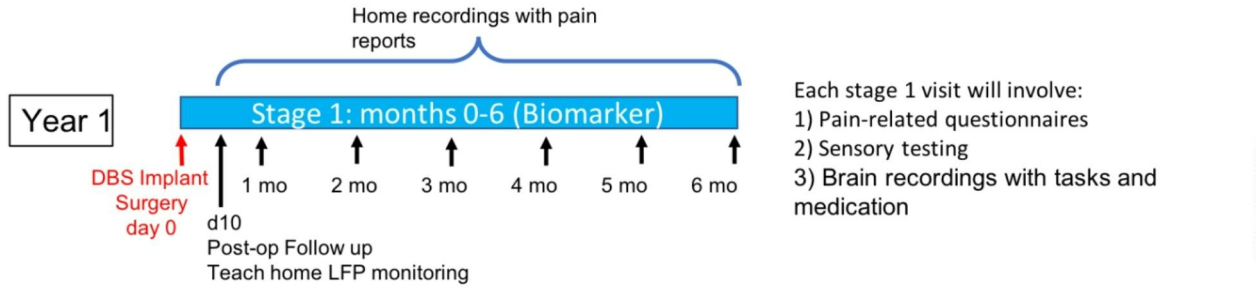

Figure 2

During DBS surgery (Surgery 2 of 2**)**

If the trial period was successful (Stage 0), we will bring you back to the hospital for the final brain surgery (see **Figure 2, Surgery-Day 0**). The second surgery will be scheduled up to 1 month after the trial electrodes were removed. Before surgery, we will check that your health status has not changed in ways that would make you not eligible for the surgery or the study.

At the end of the 10 day trial period we will remove all the wires (electrodes) that were implanted (Stage 0). After about one month, we will then implant up to 2 electrodes in place per side of your head for chronic implantation and connection to the pulse generator **(Figure 3).** If stage 0 is not performed, you will have up to 2 electrodes implanted per side of your head with connection to the pulse generator.

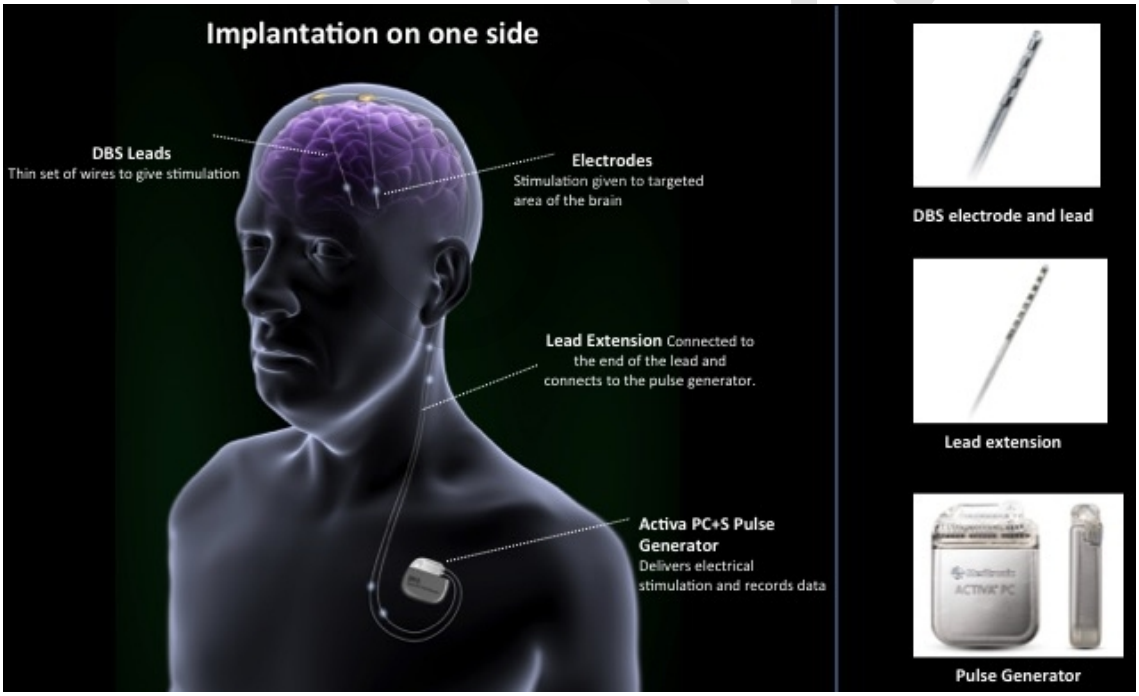

Figure 3

The DBS leads that remain in your brain will be attached to “lead extensions” and the “lead extensions” attached to a “pulse generator” called Summit RC+S, which can deliver electrical stimulation and also store recorded brain activity. The Summit RC+S is implanted in the upper chest.

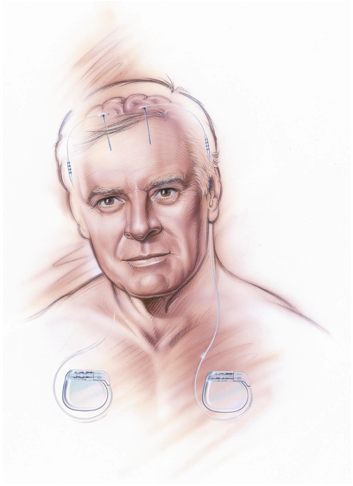

Figure 4

If you already have a pre-existing DBS implant, you will be skipping over the insertion of chronic implants and instead only undergo a procedure to remove and disconnect your current DBS implant from your implanted leads, and subsequently implanting the Summit RC+S system in the same location in the upper chest and reconnecting it to the leads already in place.

If you have one side of the brain implanted with leads, you will have one Summit RC+S generator implanted under one side of the chest (**Figure 3**). Similarly, if both sides of the brain implanted you will receive one Summit RC+S on each side of the chest, (**Figure 4**).

After the electrodes are placed, you will then undergo a head CT in the operating room under anesthesia to make sure the electrodes are in place. A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs.

After DBS Surgery

After DBS surgery is completed, and while you are recovering in the hospital, the Summit RC+S system will be tested and brain activity recordings will be performed daily in the hospital (see **Figure 2, Stage 1**). It is expected you will recover in the hospital for approximately 2-3 days. Approximately 10 days post-surgery, at wound and staple check, a data recording session will take place in an out-patient setting and questionnaires related to mood and pain will be given (see **Figure 2, Stage 1**).

You will take part in research sessions at the UCSF Medical Center regularly (approximately every month) and also collect at-home brain recordings (daily).

Stage 1: At-Home Brain Recordings

We will teach you how to record brain recordings from your home at the first out-patient visit (See **Figure 2, Stage 1, day 10, Teach at-home monitoring**).

For at home recordings, you will be given a hand-held device such as a phone or tablet computer that is not approved by the FDA for treatment, but is approved for “investigational use”. You can use this device to begin reporting of pain scores, mood scores and start brain recordings from the Summit RC+S while you are at home. We will also ask you to keep the

tablet computer or phone nearby (within 10 feet) for continuous recording over multiple hours or at night while sleeping. (Only the recording function is accessible at home. There is no way for you to accidently stimulate or activate any region of the brain with the device). You will not feel anything when the device is recording. All data collected from device, including the device itself, are encrypted.

We will make sure you feel comfortable taking the recordings before you do them at home or will make arrangements to have someone come help you.

The Summit RC+S generator is a rechargeable device, which means that you will have to recharge the battery in your chest using a wireless recharging device as often as every day, depending on battery usage. Recharging must be maintained to prevent loss of function such as recording, stimulation or therapy. This device can only be programmed by your team at UCSF using a special programmer and cannot be programmed by other physicians or other hospitals. You must be capable and willing to recharge the device. Instructions on how to do this will be conveyed by research staff. You will not feel anything when the device is recharging.

During the at-home recording sessions, you will also send pain and mood reports through text or email at home multiple times per day. Example report scales may ask you to rate your pain intensity on a scale from 0 to 10, with 0 being no pain and 10 being the absolute worst pain you have experienced. We will also ask you to report how much the pain is bothering you, on a scale from 0 to 10, with 0 being not at all bothering you to 10 completely bothering you. Other surveys will include rating scales on aspects of your mood, thinking and sleep patterns.

With your permission, study staff may arrange to go to your home to help you with initiating the data recordings. These data can be downloaded at your next clinic visit, or, with your permission, during a home visit by study staff.

We will also ask you to wear an activity tracker (e.g. FitBit) and upload your data via a smart phone application using an anonymous account (i.e. no personal identifiers will be linked to the activity tracker account).

Stage 1: Out-patient appointments (Months 1-6)

In the first part of the study (**roughly study months 1-6)**, we will be studying how brain activity differs when you are in pain versus not in pain. In these out-patient clinic study sessions, you will fill out various questionnaires in addition to undergoing brain recording sessions. The recording sessions will be done at various times and under various conditions, including at rest, during quantitative sensory testing (QST) in which you will be asked to test cold and heat sensation and cold and heat pain, and during cognitive testing task. During cognitive tasks, we

may ask you to complete a computerized task by responding to images on a screen and pressing a keyboard, or by wearing a virtual reality (VR) headset and using handheld controllers. VR uses computer technology to create a simulated experienced using motion-detecting headset and controllers. During Stage 0, this headset will be fitted around the temporary electrodes and will feel like wearing a baseball cap and goggles. While it is on you will have a 360-degree view of the simulated task setting, such as a virtual kitchen. You will be laying down, sitting, or standing while performing a simple task, such as stacking dishes. While performing this short task we will be recording from your Summit RC+S to better understand your pain fluctuation during simple tasks. We may also ask you to perform various activities, (such as standing or walking) and will take recordings before and after pain medications.

During the out-patient appointments, temporary flat electrodes may be placed on your scalp and your arm muscles. We may also use electroencephalography (EEG) or electromyography (EMG), where temporary flat sticker-like electrodes are placed on your scalp, arm/leg or fingers to help us obtain more health-related signals; this is similar to getting an EKG (electrocardiogram). These electrodes will be attached to a computer to help us record these signals alongside your brain recordings. Brain recordings will typically last from 1-2 hours under the various conditions noted above. After brain activity recordings, the stored data will be transmitted from your Summit RC+S system to a research computer using either a wireless communication interface or uploaded to a cloud-based computer.

Your pain levels will be measured during the research sessions by standardized pain scales on a tablet computer similar to the daily at-home pain score reporting.

Each patient's needs will be different, and we will work with you to minimize discomfort as much as possible. You may also have friends or family accompany you at these sessions, if it would be helpful. Each research session will last approximately 2-3 hours.

CT Scan (Stage 1, ~2 months)

In addition to research sessions, approximately two months after brain surgery, you will have a computed tomography (CT) scan of your head done in order to check that the devices are in place. A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs.

For the CT scan, you will need to lie still on a table with your head inside a large doughnut-shaped machine. The table will move and the machine will make clicking and whirring noises as the pictures are taken. Each CT scan will take about 15 minutes to a half hour.

The research sessions and at-home sessions from Stage 1 of the study will allow us to potentially figure out how brain activity causes pain symptoms.

Based on the findings from stage 1, we will then stimulate the brain in response to pain-related brain activity in stage 2. We expect stage 1 to last approximately 6 months in order to discover a

brain signal related to pain that may respond to stimulation. However, if enough data are collected before the 6-month time period and a potential signal is discovered earlier, you may start Stage 2 at an earlier time point. Likewise, if not enough data sessions are completed (at-home or in the clinic session), or if there is difficulty in detecting a signal or if a specific signal is not detected at the end of the 6-month time period, further data collection sessions, corresponding to either Stage 1 or Stage 2 may be needed.

STAGE 2: Stimulation Testing and Recording (up to 6 months)

What can you expect?

Stage 2, Study Months 7-12:

The in-clinic research sessions and at-home sessions from Stage 1 of the study will allow us to potentially figure out how brain activity causes pain symptoms.

Based on these findings, in stage 2 of the study (roughly study months 6-12, see Figure 5), we will then stimulate the brain, both in the clinic and at-home.

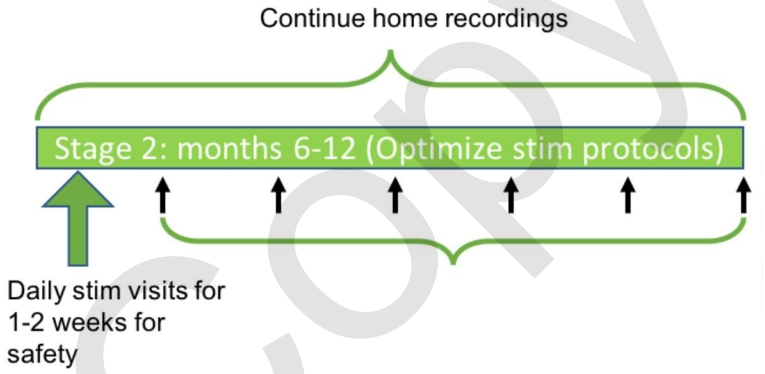

Figure 5- Black arrows indicate monthly in person visits.

We will also be studying different stimulation settings in the outpatient research sessions. Similar to Stage 1, we may also use EEG, EMG and EKG to help us obtain more data. To better detect brain signals that cause pain symptoms, you will continue to do the at-home data collection as in Stage 1.

At the beginning of Stage 2, we will conduct daily visits for the first 1 to 2 weeks to explore and safely test stimulation settings. *You will have to come to the clinic every day for up to 2 weeks.* We will then have you return to the clinic every month to do in-clinic testing with stimulation, recordings and QST with heat and cold testing, and cognitive attention testing using a computerized task as in Stage 1.

You may also be asked to take Naloxone/Narcan, a drug used to reverse the effects of specific pain medications such as Norco/Vicodin/Hydrocodone. During Stage 0, up to two, standard doses of naloxone (4mg/0.1ml) will be provided through an IV provided by the hospital for

medication delivery. During Stage 1-3, up to two, standard doses of naloxone will be administered either by inhalation through a nasal spray or by injection into the upper arm or thigh. The effects of naloxone can last up to 90 minutes. There is also a potential risk in temporary increase in pain during the naloxone administration test. You may choose to opt out of any of these tests.

When you are sent home, we will coordinate with you to change the stimulation program every 1-2 weeks to evaluate for its long-term effect. To test for possible placebo effects, we will also turn on or off your stimulation during the 1-2 week time periods in between sessions. You will not know whether stimulation is on or off. You will not feel the electrical stimulation in your brain, however you may feel your pulse generator vibrating during some stimulation. Your at-home brain recording sessions during this Stage 2 will also help us detect if there are better stimulation settings for disrupting your pain.

Stage 2 is expected to last 6 months (approximately months 7-12), but it may be possible for you to accelerate to the next phase sooner than the 6-month period, depending on various factors such as your response to stimulation, frequency of at-home recordings, etc. Likewise, Stage 2 may need to continue longer then 6 months. We will consult with you regarding length of phases depending on specifics for your individual symptoms.

STAGE 3: Comparing personalized stimulation to standard stimulation (1 year)

What can you expect?

Stage 3 (approximately months 13-24)

In Stage 3 of the study (**see Figure 6**), we will set the brain stimulation settings to be always active in an at-home setting, with close monitoring by the medical and research team and frequent out-patient visits. We will be in touch with you daily by phone for the first 2 weeks after the stimulation is turned on and you are at home, and you will continue to report pain symptoms and pain relief during this time and wear an activity monitor, such as a FitBit.

We will also have you come to the clinic every 4-6 weeks, to check on your pain and possible pain relief. During this time, we will do additional testing in the clinic and may adjust stimulation settings.

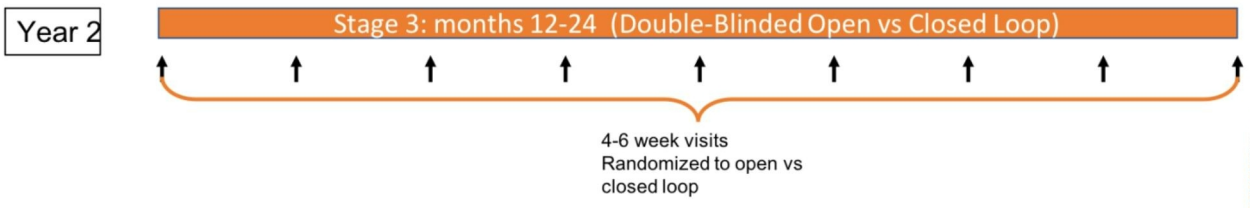

Figure 6

Specifically, the brain stimulation settings will be either in a “responsive” mode (i.e. “Closed-loop” stimulation, in which stimulation will only occur depending on your brain activity that we have found in Stage 1 and 2 that predicts your pain), or stimulation will take place in an “open-loop” manner, in which stimulation will occur continuously. “Open-loop” stimulation is stimulation that is currently in use in other medical studies and medical conditions, including off-label treatment of pain. “Closed-loop” stimulation may differ in stimulation effects than traditional “open-loop” stimulation, which we will test during Stage 3. You will be randomly assigned to one of these two modes (“open-loop” or “closed-loop” every 4-6 weeks) for year 2 of the study, months 13-24.

We will measure pain relief under these two conditions every 4-6 weeks, as well as pain-related questionnaires, brain recordings under various conditions, quantitative sensory pain testing (heat and cold sensations and pain), cognitive testing using a computerized task, naloxone administration and brain recordings before and after pain medications. You may choose to opt out of any of these tests. We may also use EEG, EMG and EKG as in stages 1 and 2.

LONG-TERM FOLLOW UP

After the study is finished (roughly 2 years), and if it is possible to leave the device on and you choose the option to leave the device on, we will follow-up with you in additional appointments, approximately every 6 weeks.

How long will I be in the study?

Being in this study will take roughly over 2 years. The study will require 2 (or more) outpatient pre-surgery visits, hospitalization / surgery #1, a stay in the sleep laboratory for up to 10 days followed by electrode removal, surgery #2, daily in-hospital visits, and up to 37 outpatient post-surgery visits for a total of about 90-130 hours of research procedure participation, in addition to daily at-home brain data recording sessions. Outpatient visits, surgery and hospitalization will take place at the pain clinic at UCSF (either at Mission Bay, Parnassus, or Mt. Zion locations). If you choose to continue having the device deliver stimulation after the study, we will have you come back to the clinic for follow-up visits (beyond the 37 outpatient study sessions) for check-ups, roughly every 6-8 weeks.

What happens to the study devices at the end of the study?

Your Summit RC+S pulse generator is expected to require surgical replacement after 9 years. When your pulse generator requires replacement, it may be replaced with Activa RC or the Percept, standard models that delivers stimulation therapy but has no ability to sense and store brain recordings, or another brain stimulation system depending on results from the clinical trial

and in consultation with your regular pain doctor. However, these other devices are usually limited to connecting with maximum two implanted leads per device, while the research Summit device can take up to four leads per device. So, if you are in the research trial with more than two implanted leads per side, one or more of the leads may not be able to connect to the new commercial device after replacement. These devices still may provide a potential therapeutic stimulation strategy in continuing to treat your pain symptoms.

If you decide, in consultation with your doctor, to leave the device in or have it replaced, you will be monitored at the clinic for out-patient appointments, approximately every 6 weeks. Please note that the Summit RC+S research device can only be programmed by the research team at UCSF using a special programmer called 'RLP.' You cannot receive reprogramming care at an institution that does not have the special RLP programmer.

If you decide to have your device replaced, costs for replacement devices after the conclusion of your participation in the research study will be the responsibility of you or your insurance provider, depending on your insurance. You can also decide to have the device turned off or removed.

In the event that you develop symptoms that your doctors think are related to the study, such as muscle weakness or seizures, then your doctors may recommend surgical removal of the device and DBS electrodes.

If you decide to continue stimulation with the implanted device after the end of the study, the investigators will continue to follow up with you for life.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study staff if you are thinking about stopping or decide to stop.

It is important to tell the study staff if you are thinking about stopping so that your doctor can evaluate any risks from the brain recording and discuss what alternative follow-up care and testing could be most helpful for you.

The study doctors may stop you from taking part in this study at any time if they believe it is in your best interest, if you do not follow the study rules, or if the study is stopped.

RISKS AND POSSIBLE SIDE EFFECTS

What side effects or risks can I expect from being in the study?

You may have side effects while on the study, though brain activity recording is not expected to cause side effects. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. We will also ask about side effects during every clinic visit.

We ask that you remain on your current pain medications without increasing or decreasing their doses. If you are receiving injections or other pain related procedures we ask that you notify the research team about the date and times of these procedures.

You should talk to study staff about any side effects that you experience while taking part in the study.

Risks and side effects related to General Anesthesia

You will need general anesthesia in order to have a deep brain stimulator implantation. There are very rare but serious side effects associated with general anesthesia including: irregular heartbeat, increases or decreases in blood pressure, rare reactions to medications used in the anesthesia, and blockage of breathing passages. Other rare complications include nerve injury, lung injury, heart attack and brain damage. An extremely rare but serious complication is rapid increase in body temperature. All of these complications are treatable but might lead to coma or even death. You will have an opportunity to discuss these risks with the anesthesiologist. There may also be unknown risks.

Risks related to brain scans

CT scans involve the risks of radiation. In addition, if contrast material (gadolinium or iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function.

MRI risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear earplugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and

can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

Risks and side effects related to both DBS surgeries are estimates based on scientific literature to date, and may include:

Likely
- Temporary pain at the surgery sites
- Temporary headache after surgery

Less Likely
- Seizures
- Infection in areas of the body in which the device comes into contact (i.e. brain, neck, chest) could lead to irritation or life-threatening illness which would require further surgery to remove all or parts of the device. Risks of removing the device may involve temporary pain at the surgery sites and temporary headache after surgery.
- Erosion of the device through the skin covering it, requiring further surgery to cover or remove the device
- Confusion or attention problems
- Temporary motor deficits

Rare but Serious
- Bleeding inside the brain (stroke), that could cause paralysis, coma, or death
- Harmful reaction to anesthetic agents
- Leaking of the fluid surrounding the brain
- Air embolism (air bubble that enters an exposed blood vessel on the surface of the brain or in the skull bone, which can travel to the heart and possibly lung, a potentially life-threatening condition).

Risks and side effects related to implanted DBS electrodes:

Likely
- A risk and side effect related to implantation of the DBS electrodes is that you should not have MRIs while the electrodes are implanted, and it will be important that you remember to inform any health care provider who is considering MRI that you have implanted DBS electrodes that makes MRI unsafe for you. Brain injury can occur from having MRI scans with an implanted stimulation system. Placement of two leads in one hemisphere is off-label (i.e. not recommended) for MRI. If you are in this study and require an MRI scan of the brain for important medical reasons, your doctors will determine if the reason for brain MRI is important enough to proceed. MRI scans are used to evaluate and diagnose a variety of symptoms and health problems, therefore you may experience a health problem that is harder to diagnose because you should not have an MRI.
- You should also not undergo diathermy (high-frequency electrical current treatment, used often in treatment of arthritis) with implanted DBS electrodes and Summit RC+S pulse generators.

Rare but Serious

- Possibility of damage to the brain from inserting a long-term electrode on the brain surface producing muscle weakness or seizures.

Risks and side effects related to brain activity recording are estimates based on scientific literature to date, and may include:

Likely

- Possible worsened pain symptoms after holding pain medications before some study visits, although the study will attempt to minimize altering medication schedules.

Less Likely

- If you have two pulse generators implanted instead of one, you may have a small increased risk of post-surgery pain; infection due to an additional surgical site and an additional surgical scar. There is also potential for increased infection and pain associated with multiple leads (i.e. greater risk with 4 leads versus 2 leads).
- Possibility that the pulse generator will fail to deliver brain stimulation that will effectively treat pain symptoms. The device contains the identical therapeutic stimulation components as those in the FDA approved device and would be expected to function with the same level of reliability; however additional sensing technology has been added, making the device experimental. Thus, as an experimental device, with additional sensing circuits that have not yet been approved for use in humans, there is a possibility that performance might not match the standard device. The actual risk of less effective brain stimulation is unknown.

Risks and side effects related to long-term DBS therapy are estimates based on scientific literature to date, and may include:

Less Likely

- The brain electrodes or lead/extension connectors may move. Further surgery to re-adjust the location may be needed.
- Components or parts of the brain stimulation system may suffer mechanical breakage resulting in loss of therapy. Further surgery to replace the system parts may be needed.
- The brain stimulation system could stop because of an electrical or software malfunction, which could require further surgery
- Battery in the pulse generator could run out. This would require further surgery. Pulse generator battery life depends on individual use, but for most device use, batteries should perform for more than 6 years.
- There may be an allergic reaction to the brain stimulation system. The system materials coming in contact with the tissues include titanium, polyurethane, silicone, and nylon. The body could also reject the system (as a foreign body).
- There is the possibility of tissue damage resulting from the programming settings or a malfunction of one of the parts of the brain stimulation system.
- Turning on the stimulator may produce side effects such as difficulty with speech, increased pain, abnormal sensations, dizziness, confusion, change in mood, thinking or emotions, or abnormal eye movements. It may have side effects that are unknown.

Other Rare but Serious Risks

Thoughts of suicide: The possibility of suicidal thinking will be monitored throughout the study with questionnaires administered by the investigators. The study investigators will also be contacting you and your psychiatrist/psychologist every week to assess whether any thoughts of suicide come up. If you experience thoughts of suicide, tell the investigators and they will provide you with a mental health referral.

Reproductive risks: The reproductive risks of participating in this study are unknown. Women who are breastfeeding or potentially could become pregnant will not be allowed to participate in this study.

Radiation risks: This research study involves exposure to radiation. Not all this radiation exposure is necessary for your medical care and is for research purposes only. The additional amount of radiation that you will receive as a result of participating in this study is equivalent to 2 times the yearly natural background of radiation in the US. This amount of radiation may involve a low risk of cancer. If you are pregnant, you SHOULD NOT participate in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.

Possible increased pain: may occur during Stage 2 in which placebo (i.e. no stimulation) sessions are used. You will be closely monitored during the study and efforts will be made to decrease any periods of the study associated with possible increased pain. There is also a potential risk in temporary increase in pain during the naloxone administration test.

Unknown Risks: Brain recording may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

Stimulation of multiple brain regions at the same time has been performed in the past using DBS and other brain stimulation technologies. However, because the brain regions we may use for stimulation in this study are new, there are unknown risks related to the combined stimulation of these multiple regions.

Possible Device Complications

There may be pain, lack of healing, or infection where the brain stimulation system parts are implanted. If this happens, further surgery or removal of part of the system may be necessary.

The brain's stimulation system parts may wear through the skin, which can cause an infection or scarring.

The brain leads or lead/extension connectors may move. Further surgery to re-adjust the location may be needed.

Components or parts of the brain stimulation system may suffer mechanical breakage resulting in loss of therapy. Further surgery to replace the system parts may be needed.

The brain stimulation system could stop because of an electrical or software malfunction, which could require further surgery if noninvasive attempts to restore the software did not succeed.

The recharge capacity or 'cycle life' of the pulse generator could be prematurely depleted. This would require further surgery. Pulse generator battery service life depends on individual use. It has been shown for most patients with Parkinson's disease that the RC+S IPG should be usable for up to 9 years without replacement.

There may be an allergic reaction to the brain stimulation system. The system materials coming in contact with the tissues include titanium, polyurethane, silicone, and nylon. The body could also reject the system (as a foreign body).

There is the possibility of tissue damage resulting from the programming parameters or a malfunction of one of the parts of the brain stimulation system.

The RC+S device is a rechargeable device and like the standard RC pulse generator. If you forget to recharge the unit, you may be temporarily without DBS stimulation. Also, there is the possibility of generator malfunction specific to Summit RC+S; leading to premature battery drain or need to recharge the battery more frequently, due to sensing function capability

Risks specific to patients previously implanted with the Activa PC+S system participating in this protocol and undergoing battery replacement with Summit RC+S

The surgical risks related to battery replacement are similar to the risks related to initial implantation of the battery as part of DBS surgery above, however, you may experience pain in the region of battery replacement for up to 1 week.

There is a risk of being unable to reprogram or deactivate the RC+S device with commercially available Medtronic hardware, because the RC+S device requires a special programmer that many hospitals and clinics do not have on hand. The RC+S device can still be deactivated by the patient's own programmer.

There is a risk of battery depletion of RC+S if you forget to recharge the device, since it is not a primary cell device.

Risks and side effects related to removal of some electrodes or total <u>removal</u> of the DBS electrodes and device

<u>Likely</u>

- Temporary pain at the surgery sites
- Temporary headache after surgery

<u>Less Likely</u>

- Seizures
- Infection in areas of the body in which the device comes into contact (i.e. brain, neck, chest) could lead to irritation or life-threatening illness which would require further surgery to remove all or parts of the device. Risks of removing the device may involve temporary pain at the surgery sites and temporary headache after surgery.
- Confusion or attention problems

Rare but Serious

- Bleeding inside the brain (stroke), that could cause paralysis, coma, or death
- Harmful reaction to anesthetic agents
- Leaking of the fluid surrounding the brain
- Air embolism (air bubble that enters an exposed blood vessel on the surface of the brain or in the skull bone, which can travel to the heart and possibly lung, a potentially life-threatening condition).

Risks and side effects related to cognitive task testing

The use of current technology, such as computer and tablet screens, may cause eye strain, eye dryness, temporary blurred vision, and headache. Virtual reality headsets may also cause headaches, eye strain, dizziness, and nausea. These computer-based tasks will involve frequent breaks, and you will able to pause or stop participation at any time.

For more information about risks and side effects, ask your study doctors.

Are there benefits to taking part in the study?

There will be no direct benefit to you from participating in this study, although one of the goals of the study is to provide pain relief. Pain treatment from using the Summit RC+S has not yet been shown, but DBS with similar systems have been shown to give pain relief for certain patients. This study will help doctors learn more about how DBS may affect brain activity related to pain, and it is hoped that this information will help in the treatment of future patients with chronic pain. After the study ends, you will also have a choice to have the device remain implanted (and also after consultation with your doctors) if you have experienced pain relief from the study.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting standard pain treatment without being in a study.
- Other pain treatment alternatives such as different classes of pain medications, spinal injections, spinal cord stimulation and / or drug pump medical devices.

Please talk to your doctors about your choices before deciding if you will take part in this study and other options for pain treatment that are available to you.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

If suicidal thinking is identified during routine study monitoring, you will be referred for urgent psychiatric evaluation, which may involve a loss of privacy.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Representatives of Medtronic, Inc., the company that makes the Summit RC+S device
- Representatives of the National Institutes of Health
- Representatives of the University of California
- Representatives of Food and Drug Administration (FDA)
- Members of the Data and Safety Monitoring Board for this study, including Drs. Vikram Rao, Daniel Lu, Nicholas Schiff, Cynthia Kubu, and a psychiatrist who does not have direct involvement in this study but who has expertise in implantable devices, pain management and neurosurgery.

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

Will I be paid for taking part in this study?

For visits starting 10-days after surgery (a total of up to 37 visits), you will be reimbursed at the IRS rate for mileage driven from your home to UCSF and back. If you do not have a handicap placard, we will provide parking stickers to pay for parking at the UCSF parking garage. For patients living more than 60 miles away, you will be reimbursed for 1 night hotel charge up to $200 on the night before each visit and 1 round-trip flight up to $400.

What happens if I am injured because I took part in this study?

It is important that you tell the research staff and / or your study doctor, Edward Chang, MD or Prasad Shirvalkar, MD PhD, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him or the research staff at 415-502-1653, Monday through Friday, 8AM to 6PM (Pacific Standard Time).

Once eligibility has been established and you are officially enrolled in the study (before undergoing hospitalization and / or surgery), you will be given a contact number where you can access a physician pager service after hours and on weekends, if you feel an injury has occurred after hours.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, treatment will be available. The costs of the treatment may be covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office

of the Institutional Review Board at 415- 476-1814.

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

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

When will the study be STOPPED due to serious side-effects?

If any of the below criteria are met the study will be halted for all subjects until information is reviewed by the DSMB and FDA:

a) Death from any cause in one patient
b) Irreversible neurologic damage in one patient
c) Suicide attempt in 2 or more patients
d) Suicidal ideation requiring hospitalization in 2 or more patients
e) Failure of 5 patients to advance past the Trial 0 screening to Stage 1 implantation.

Surgical implantation of new or current patients will be halted if any of the below criteria are present until information is reviewed by the DSMB and FDA. Data collection may continue in already implanted patients.

f) More than 3 patients develop symptomatic bleeding in the brain
g) Brain swelling or symptoms that do not resolve with a month of onset in 2 patients.
h) Infection requiring hospitalization or extend the post-surgery period for more than a week in 2 patients.
i) Confusion lasting more than 2 weeks in more than 2 patients
j) 2 patients that develop post-surgery seizures without a previous diagnosis of seizure disorder.
k) Worsening neurological status related to the study as judged by the study doctors

Who can answer my questions about the study?

You can talk to research staff related to the study or your study doctors about any questions, concerns, or complaints you have about this study. Contact the research study at chronicpain@ucsf.edu or at 415-502-1653.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have

about the study, please call the Office of the Institutional Review Board at 415-476-1814.

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.