**TUFTS MEDICAL CENTER**
**TUFTS UNIVERSITY**
**Ophthalmology Department**

# INFORMED CONSENT TO PARTICIPATE IN RESEARCH

## Assessing the Efficacy of Intranasal Neurostimulation in Ameliorating Symptoms of Neuropathic Corneal Pain

Principal Investigator: Pedram Hamrah, MD
Co-Investigators: Gabriela Dieckmann, MD, Neslihan Dilruba Koseoglu, MD, Anam Akhlaq, MBBS, William Binotti, MD, Stephanie Cox, OD

Study team telephone number: 617-636-5720

## INTRODUCTION

You have been invited to take part in a clinical research study. To keep the information in this form simple, we shall refer to a clinical trial as a research "study". The research staff will explain the study to you. You will be informed of the purpose of the study, what is required of you, and any potential risks or benefits of participating.

You are being asked to participate in this study because you have symptoms of neuropathic corneal pain (NCP).

Taking part in this research study is entirely your choice. You can refuse to participate in this study. If you decide to participate in this study, you can then choose to stop taking part in the study at any time for any reason. If you refuse to participate in the study or stop being in this study, it will not affect your care or treatment outside this study, payment for your health care, or your health care benefits.

Please read all of the following information carefully. Ask Dr. Hamrah, or his representative, to explain any words, terms, or sections that are unclear to you. Ask any questions that you have about this study. Do not sign this consent form unless you understand the information in it and have had your questions answered to your satisfaction.

If you decide to take part in this research study, you will be asked to sign this form. You will be given a copy of the signed form. You should keep your copy for your records. It has information, including important names and telephone numbers, to which you may wish to refer in the future.

If you are eligible to participate and decide to be in the study, Dr. Hamrah may still choose to stop your participation in this study if he thinks it is in your best medical interest.

New things might be learned during this study that you should know about. The investigators will tell you about new information that may affect your willingness to stay in this study.

If you withdraw or are withdrawn from the study, any data collected from you before your withdrawal will still be used for the study.

As a participant in this study, your identity, medical records, and data relating to this study will be kept confidential, except as required by law.

If you have questions about your rights as a research study subject, call the Tufts Medical Center Health Sciences Institutional Review Board (IRB) at (617) 636-7512. The IRB is a group of doctors, nurses, and non-medical people who review human research studies for safety and protection of people who take part in the studies. Federal law requires the IRB to review and approve any research study involving humans. This must be done before the study can begin. The study is also reviewed on a regular basis while it is in progress.

This research study has been reviewed and approved by the IRB of Tufts Medical Center and Tufts University Health Sciences.

**PURPOSE OF STUDY**

The purpose of this study is to find out if the use of an intranasal tear neurostimulator (ITN) may be useful in improving the pain symptoms felt by patients who have neuropathic corneal pain. The intranasal tear neurostimulator (ITN), called TrueTear®, is the first and only FDA-cleared device developed to temporarily increase tear production during neurostimulation in adult patients. It has been shown to be safe and effective for temporarily increasing tear production in adult patients in two clinical trials. Currently, you need a prescription from your eye doctor to use the TrueTear® device. This device will be returned back to the study once it is over. If you would like to continue the use of the TrueTear® device once the study is over, please talk to your eye doctor.

The secondary aims of this study are to:

- To see if the use of ITN is safe, effective, and long-lasting in improving the pain symptoms in patients with NCP with daily use.
- To find quality of life changes by treating NCP with ITN during short and long term daily use.

55 subjects will be screened in order to have 45 subjects enrolled and complete this study at Tufts Medical Center. Allergan is sponsoring the study, which is initiated by the Principal Investigator. All study activities will be conducted here at Tufts Medical Center where Pedram Hamrah MD is the Principal Investigator.

**PROCEDURES TO BE FOLLOWED**

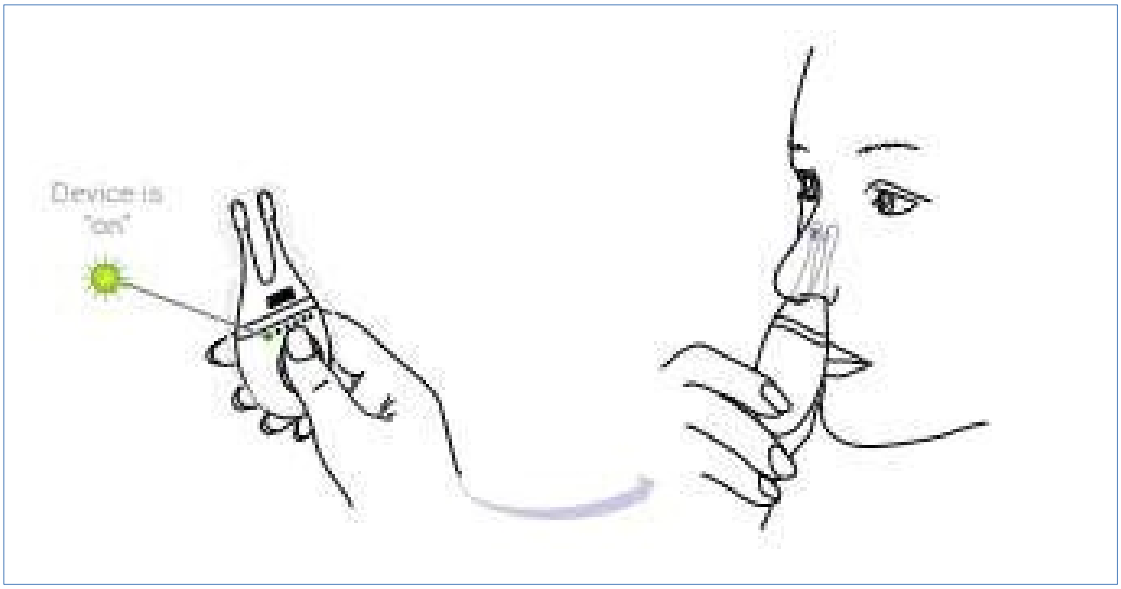
If you decide to participate in this study by signing this consent form, you will be screened to check if you qualify for the study. If the screening tests show that you are eligible, you will continue in the study as described below. If you are determined to be ineligible, the data

collected about you will not be included in the study. Any data collected at the beginning of the study before you withdraw will still be used in the research.

If you participate in this study, you will be trained on how to use the intranasal tear neurostimulator (ITN), called TrueTear®, properly.
You will use the TrueTear® a minimum of at least twice a day. If you need to use it more often that twice a day, you can.

**TrueTear® Intranasal Neurostimulator (ITN).**
You will be instructed to place the tips of the ITN into both nostrils simultaneously. You will be asked to apply and control the intensity of stimulation by pressing the plus (+) or minus (-) buttons on the device. You can choose the level of intensity from 1 to 5. You will be asked to apply it for 3 minutes [could be modified if need be]. You can also control the location of stimulation by the depth and angle of insertion until you feel a "tickle" sensation. You can cease stimulation by pressing the minus button on the Base Unit or by withdrawing the entire device from the nostrils.

We will also provide you with a brochure explaining these directions for you to take home.




**Use of the TrueTear® Intranasal Neurostimulator (ITN).**
**Turning on the device and placing it into the nose**

If you have any of the following conditions or implants, you are not eligible to participate in this study, as the TrueTear® Intranasal Neurostimulator (ITN) should **not** be used:

- A cardiac pacemaker, implanted or wearable defibrillator, or other implanted metallic or electronic device such as a cochlear implant, in the head or neck
- Chronic or frequent nosebleeds, a bleeding disorder, or another condition that can lead to increased bleeding

- A known allergy to the hydrogel materials that comes into contact with the inside of your nose.

The ITN delivers small electrical currents to the inner cavity of the nose, gently activating nerves that stimulate the body's natural tear production system.
The device consists of four distinct parts (Figure 1):

1. A reusable Base Unit which produces the electrical stimulation waveform.
2. A disposable Tip Assembly that inserts into the nasal cavity and stimulates the target intranasal tissue.
3. A reusable Cover to protect the Tip Assembly.
4. A Charger which recharges the battery inside the Base Unit.

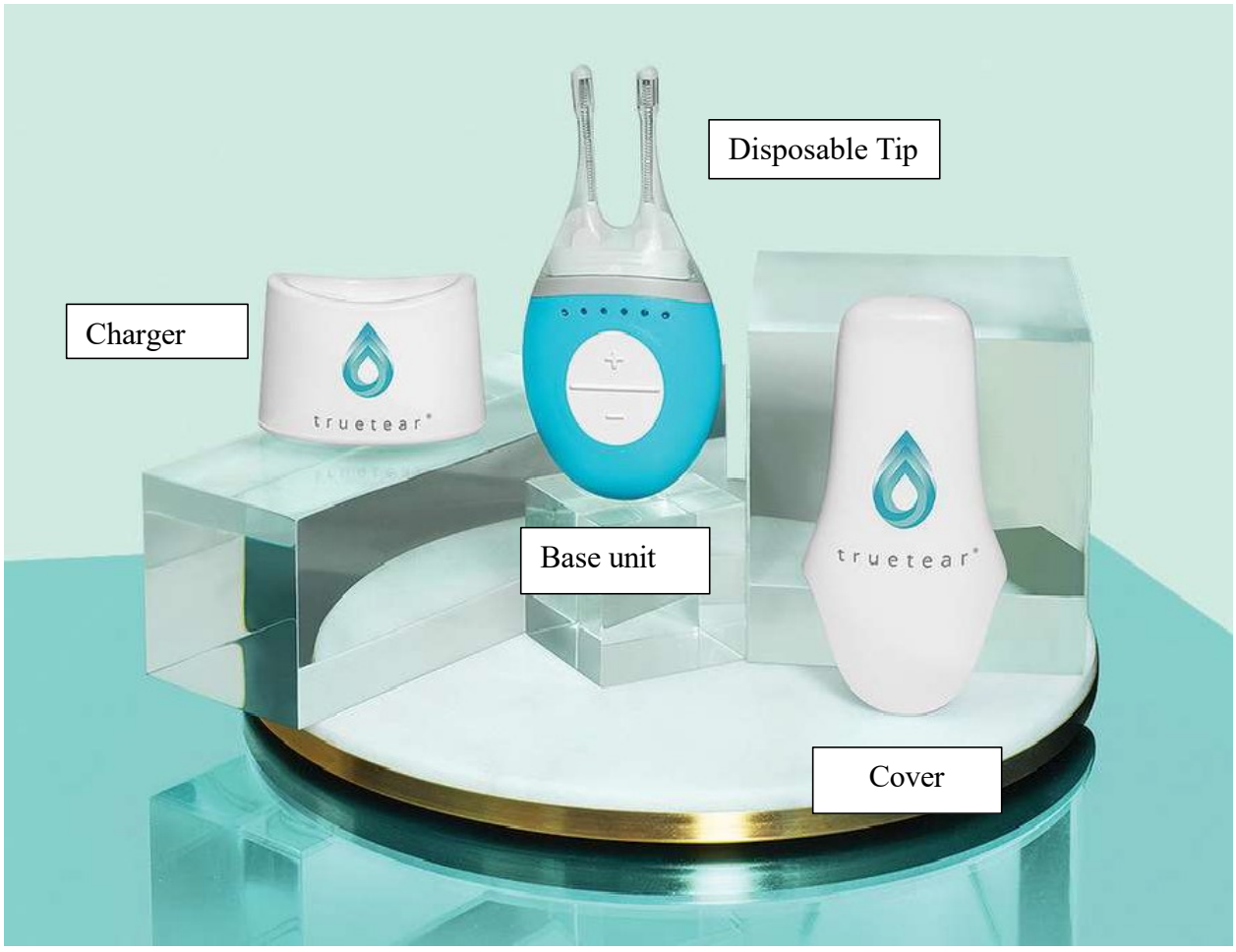



**Figure 1: The TrueTear Intranasal Neurostimulator (ITN) components.**

**1. Base Unit**

When activated, the base unit provides electrical pulses to the Tip Assembly. The strength of these pulses is controlled by two buttons, with five different levels available, indicated by the number of illuminated LEDs on the base unit. The Base Unit can only be activated when a Tip Assembly is present. The base unit also records the use of the device, stimulation level and duration, in internal memory.

**2. Tip Assembly**
The Tip Assembly is specially designed to allow the participant to easily apply stimulation to the target areas within the nose. The Tip Assembly connects to the Base Unit and contains a hydrogel (similar to the material used in contact lenses) that touches the inside of the nose to provide stimulation. The disposable Tip Assemblies are removed and replaced at least daily; a separate Cover can be used to protect the Tip Assembly when not in use.

**3. Cover**
The cover may be slipped over the top of the Base Unit and Tip Assembly between uses.

**4. Charger**
The Base Unit may be recharged by removing the Tip Assembly and placing it onto the Charger. Charging takes under 4 hours, and a green LED indicates that the process has completed.

We will ask you questions at every visit about your usage of the ITN. You will be asked to complete a diary every day to record any pain symptoms. You will be asked to send your pain diary weekly to the study coordinator, in however method works for you, such as phone call, online survey, email, or mail. If you prefer to mail, we will provide self-addressed envelopes for you to send back the diaries If you prefer to email your responses, we will email you when it is time to complete your diary. If you prefer to complete an online survey, we will send you a link to the survey when it is time to complete your diary.

**Screening Procedures (~1 – 1.5 hours)**
Participation in this study involves your routine office visit to the New England Eye Center at Tufts Medical Center. These procedures can be completed on the same day. The following evaluations and procedures will be performed during the screening period to see if you qualify for this study:

1. Written informed consent
2. Record of current ocular and systemic medications including eye medications currently taking.
3. Record if you have any significant medical/surgical history in the past 5 years
4. Record your demographic data, including date of birth, sex, and race/ethnicity
5. Eye examination
    - You will be asked to read an eye chart while wearing your glasses or contacts or corrective lenses
    - We will look at the front of the eye with a microscopic lamp
    - We will also check pressure inside the eye

- We will drop a fluorescein drop (a dye to look at changes on your cornea) to both eyes. After several blinks, the tear film will be examined. (Tear Film Break Up Time (TBUT))
- A strip of fluorescein (yellow) dye will gently touch the conjunctiva (white part of your eye), to stain the cornea (transparent part of the eye). You will then be examined by microscopy lamp (corneal fluorescein staining)
- A strip of Lissamine (green) dye will gently touch the conjunctiva (white part of your eye), to stain the ocular surface. You will then be examined by microscopy lamp (Lissamine Green staining)

6. Imaging (In vivo confocal microscopy examination (IVCM)): This is a non-invasive standard of care imaging technique that allows us to see the cornea with 800x magnification, using a scanning laser. The laser is used to map a small area of the conjunctiva (white part of the eye), and will not damage or harm your eye. Studies have shown that IVCM can be used to study cells within the conjunctiva. IVCM has recently been used at Tufts Medical Center to assess the extent of eye inflammation in cases of dry eye and corneal neuropathy patients.
7. Complete a short questionnaire about your eye symptoms and quality of life

**Enrollment/Baseline Procedures(~20 minutes)**
Once screening procedures complete your information will be evaluate and it will be determined whether you are eligible to participate. If you are eligible to participate, the following baseline procedures will be performed. This study visit will occur immediately after the screening assessments.

1. **Filter glasses:** This test will be done in a dimly lit room, one by one for both eyes. We will cover one of your eyes, first so that you cannot see any light. For the other eye, you will look through a lens, while light will be shone on to your eye. Then, we will change the filters for the lens, such that every subsequent filter increases the level of light for your eye. We will ask you if you feel discomfort or pain at any filter (Visual Analogue Scale (VAS)). This test should take approximately 5 minutes.
2. **Hyperosmolatity response**: We will topically apply one drop of 5% sodium chloride (Muro 128® 5%) drop onto your eyes. Your level of discomfort/pain will be assessed by a questionnaire before and after the drops are applied (Visual Analogue Scale (VAS)). This test should take approximately 1 minute.
3. **Cold response test:** We will topically apply one drop of cold 0.9% preservative-free saline eye drops onto your eyes. You will be asked if you feel any change in discomfort or pain before and after the drops (Visual Analogue Scale (VAS)). This test should take approximately 1 minute.
4. **Proparacaine Challenge Test:** We will topically apply one drop of a numbing drop (Proparacaine hydrochloride ophthalmic solution (Alcaine®, 0.5%)) drop in both eyes. You will be asked if you feel any change in discomfort or pain before and after the drops (Visual Analogue Scale (VAS)). This test should take approximately 1 minute.

**Schirmer's test**: The end of a special paper strip will be placed inside the lower eyelid of each eye. Both eyes are tested at the same time. Before the test, you will be given numbing eye drops to prevent your eyes from tearing due to irritation from the paper strips. You will be asked to

close your eyes for 5 minutes, after which we will remove the paper and measure how much of it has become moist.

**Standard of Care Visits**

If you come to the Cornea Department for a visit that is not related to the study (for example a glasses prescription change), your regular eye doctor will make a note of any changes in your eyes and report this to the study doctors only if your symptoms are worsening.

**Main Study Procedures (including Follow-Up)**

There are 3 total visits in this study. All visits will take place at the New England Eye Center at Tufts Medical Center.

**Screening/Enrollment/Baseline** (~2 hours):

- Screening: All of these procedures are standard of care, meaning these happen as part of your routine care at the eye doctor. We will collect the following information during this visit:
  - Record of medications, medical and surgical history, demographics
  - Eye examination (best corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure)
  - Corneal fluorescein staining
  - Conjunctival lissamine green staining
  - Tear break up time (TBUT)
  - Central corneal *in vivo* confocal microscopy (IVCM)
  - Questionnaires about your eye symptoms, quality of life and Safety and tolerability questionnaires
- Enrollment/Baseline: These procedures are done if you are eligible to join the study. These are done for research purposes.
  - Functional nerve tests (filter glasses, cold response, hyperosmolarity response, proparacaine challenge test) with pain scale questionnaire
  - Schirmer's II test

**Visit 1** (same day as Screening/Enrollment/Baseline if eligible) (~30 minutes). You will be taught how to use the ITN in the office before administering your first dose to yourself. The ITN will be provided to you; and you will be instructed how to complete the diary to keep readings. You will be asked questions about pain and light sensitivity when using the ITN.

**Visit 2** (6 weeks) (~1 hour) – this is a visit will be around 45 days after Visit 1. All of the procedures done at the screening/baseline visit will be done in the 2nd visit (except confocal microscopy). All of these procedures are standard of care, meaning these happen as part of your routine care at the eye doctor.

**Visit 3** (3 months) (~2 hours) – this visit will be around 90 days after Visit 1. All of the procedures done at the screening/baseline visit will be done in the 3rd visit. All of these procedures are standard of care, meaning these happen as part of your routine care at the eye doctor.

We will also ask you about your general health and any adverse experience with the study at the each study visit.

**Unscheduled Visits**
If you come to the Cornea Department for a visit that is not related to the study (for example a glasses prescription change), if the study is still ongoing, we will make a note of any changes in your eyes and report this to the study doctors only if you have other adverse events.

**Early Termination**
If you withdraw or are withdrawn from the study before you complete all study visits, there will be no additional procedures performed. Your information/data obtained for this study will remain in the study for the purpose of data analysis.

**RISKS**

The following are risks that may occur with participation in this study:

TrueTear® Intranasal Neurostimulator (ITN): You may feel tingling or sneezing sensation with its use. No adverse effects are anticipated from the instillation of eye drops or gels used during confocal microscopy. You might feel burning for a few seconds after installation of anesthetic drops. You may also have nosebleeds, numbness, or infection of the nose. You may experience headaches, facial pain, and sensation of teeth vibrating. You may also get excessive runny nose, increased saliva production, and temporary increase in nasal allergies symptoms.

Cornea in vivo confocal microscopy (IVCM): The IVCM scanning machine is used routinely in the clinic for taking pictures of the cornea and conjunctiva. No adverse effects are anticipated from the instillation of eye drops or gels used during this procedure. You might feel a mild burning for a few seconds after installation of anesthetic, cold, or hyperosmolar drops. The test will be stopped if you experience any discomfort despite the use of anesthetic (numbing) eye drops. There could be an accidental scratch of the cornea during confocal microscopy, but this is highly unlikely in the hands of an experienced technician.

Allergies: If you are allergic to benzalkonium chloride “BAK” (an eye-drop preservative), you will not be able to participate in this study. Using BAK while allergic could cause disruption of tar film and possible damage to the cells on the surface of the eye.

Colored dyes: The fluorescein and lissamine green dyes may cause some irritation to eyes, and make skin and bodily secretions and excretions (such as tears or mucous) to change color. These effects are temporary and will disappear within 24 hours. There will be no psychological or radiation risks.

Confidentiality: Possible loss of confidentiality.

Inform your study doctor right away if you experience any side effects.

**BENEFITS**

There is no direct benefit to you from participating in this study. However, this study may help us understand if an Intranasal Neurostimulator (ITN) may be beneficial in assisting with pain in patients with NCP.

**ALTERNATIVES**

You may choose not to participate in the study. If you choose not to participate, you will still receive routine standard of care. The ITN is currently available by a doctor's prescription only.

**RESEARCH RELATED INJURY**

It is important that you tell your study doctor if you feel that you have been injured because of taking part in this study.

Emergency medical treatment will be given to you if you are hurt or get sick as a direct result of being in this research study. You or your insurance carrier will be required to pay for any such medical care. Any needed medical care is available at the usual cost. All needed facilities, emergency treatment, and professional services are available to you, just as they are to the general public.. You are not being asked to release or waive any of your legal rights against the institution, the study investigators or the sponsor for liability for negligence. Neither the institution nor the study sponsor will pay for your treatment if you become ill or injured as part of this study.

**COSTS**

Your eye exam at the screening visit, and the imaging for this study (IVCM) at your screening visit and Visit 3, are considered to be standard of care and will be billed to you or your insurance company. The ITN will be provided to you at no charge to you during the study participation.

**PAYMENT**

You will not be paid for your participation and time in this study. The ITN will be not be yours to keep once the study is over. You have to return the device back to us.

**PRIVACY AND CONFIDENTIALITY**

Tufts Medical Center will take reasonable measures to safeguard the confidentiality of information that identifies you and relates to your past, present, and future physical and mental health and conditions (protected health information) collected, used and shared as part of this research as required by the federal Health Insurance Portability and Accountability Act (HIPAA). Research data will be coded using a subject's identification number that does not include the subject's initials and is not derived from the subject's identifiable information. Paper

files will be locked in cabinets when not in use. Paper files will be protected from inappropriate access when in use. Only the research staff will have access to such files.

Information derived from this study may be used for research purposes that may include publication and teaching, but will not be used for studies not related to this research. However, information used for publication and teaching will not disclose your identity.

For you to be in this research study, we need your permission to collect, use and share health information that identifies you, (your "health information") which may include one or more of the following:

- Demographic information, such as, but not limited to, your name, date of birth, address and other contact information such as telephone, fax, or e-mail address, gender, insurance information and social security number.
- The results of medical tests, questionnaires and interviews.
- Information from your medical record, including your medical record number.

We will only collect, use and share information that is needed for the research.

If you decide to take part in this research study, your personal information will not be given to anyone unless we receive your permission in writing. It will only be given if the law requires it. It will also only be given for regular hospital treatment, payment, and hospital management activities.

We will make every effort to keep your information private, but it cannot be completely guaranteed. Certain government agencies, including Office for Human Research Protections, Department of Health and Human Services and the Institutional Review Board of Tufts Medical Center, may check records that identify you. This might include your medical or research records and the informed consent form you signed. The records of this study might also be reviewed to make sure all rules and guidelines were followed.

A description of this clinical trial will be available on http://www.Clinical Trials.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.

**AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION**

If you sign this document, you give permission to the Principal Investigator named above and research staff at Tufts Medical Center as well as other individuals at Tufts Medical Center who may need to access your information to do their jobs (such as for treatment, payment (billing) or health care operations) to use or disclose (release) your health information that identifies you for the research study described above.

The parties listed in the preceding paragraph may disclose the health information described below to the following persons and organizations for their use in connection with the research study:

- Individuals or organizations working under the direction of the Principal Investigator(s) for the study.
- Outside individuals or entities that have a need to access this information to perform activities relating to the conduct of this research, such as analysis by outside laboratories on behalf of Tufts Medical Center .
- Other researchers and institutions that are conducting or participating in this study,
- The Office for Human Research Protections in the U.S. Department of Health and Human Services, and other federal and state agencies that have the right to use the information as required by law.
- The members and staff of any Institutional Review Board (IRB) that oversee this study.

The health information that we may use or disclose (release) for this research study includes all information in your medical record related to the diagnosis and management of your dry eye disease, including the record of your care, as well as any information collected or created during the course of this study.

Tufts Medical Center is required by law to protect your health information. By signing this document, you authorize Tufts Medical Center to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them. You may not be allowed to see or copy the information described on this form as long as the research is in progress, but you have a right to see and copy the information upon completion of the research in accordance with hospital policies.

Tufts Medical Center may not withhold or refuse to provide you with clinical care based on whether or not you sign this form.

This authorization does not have an expiration date. You may change your mind and revoke (take back) this authorization at any time. Even if you revoke this authorization, this site's clinical, administrative and research staff may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this authorization, you must write to: Tufts Medical Center HIPAA Privacy Officer for Research, 800 Washington Street, Box 5100, Boston, MA 02111. If you revoke this authorization, you may no longer be allowed to participate in the research described in this form.

**WHOM TO CONTACT**

You are free to ask any questions you may have about the study or your treatment as a research subject. Further information about any aspect of this study is available now or at any time during

the course of the study from the principal investigator, Dr. Pedram Hamrah as well as all of his co-investigators at 617-636-5720 during the day, and at 617-636-5114 after normal clinic hours.

**Documentation of Consent**

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered to my satisfaction. I agree to take part in this study.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to stay in this research study.

_____ _____

Date Participant's Signature

I have fully explained to _____ the nature and purpose of the above-described study and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____

Date Principal Investigator or Representative's Signature