**INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY**

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| **Sponsor / Study Title:** | **Ahmed Kayssi - East Toronto Vascular Clinic / "Adjunctive ToeFX Photodynamic Therapy for Chronic Venous Leg Ulcers: A Single-Arm, Open-Label Pilot Feasibility Study"** |
| **Protocol Number:** | **0001** |
| **Principal Investigator: (Study Doctor)** | **Ahmed Kayssi, MD, MSc, FRCSC** |
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**NOTE FOR SUBSTITUTE DECISION-MAKERS (LEGALLY AUTHORIZED REPRESENTATIVES):**
As the participant's Legally Authorized Representative (LAR), you are being asked to provide informed consent as they are unable to provide consent for themself. If the participant regains the capacity to consent for themself, your consent for them will end and they will be asked to provide their own consent to continue participation. Throughout this form, "you" means the participant you are representing.

**INFORMED CONSENT**

You are being invited to consider participating in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood.

This form explains the purpose of this research study, provides information about the study, the tests and procedures involved, possible risks and benefits, and the rights of participants.

You may take as much time as you wish to decide whether or not to participate. Feel free to discuss it with your friends and family, or your family doctor. The study staff will tell you if there are any study timelines for making your decision. Please ask the study staff or one of the study doctors to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study. If you wish, someone may be available to verbally translate this form into your preferred language.

Participating in this study is your choice (voluntary). You have the right to choose not to participate, or to stop participating in this study at any time without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care.

**INTRODUCTION**

You are being asked to consider participating in this study because you a chronic venous leg ulcer that you are receiving treatment for.

Chronic venous leg ulcers can be painful and prone to infection. They can significantly limit a patient's function, mobility and quality of life.

**WHAT IS THE USUAL TREATMENT?**

The usual treatment can include compression therapy, regular debridement, moisture-balanced dressings, and infection management. Even with standard of care treatment, many ulcers become chronic, and recurrence rates after healing are high.

**WHY IS THIS STUDY BEING DONE?**

A major contributor to delayed wound healing is persistent bacteria, including bacterial biofilm. A biofilm is sticky outer shield that colonies of bacteria or fungi produce that makes them resistant to antibiotics and other microbial medicine. Treatments that can penetrate the biofilm to kill and clear the bacteria are important for helping wounds heal more quickly.

The purpose of this study is to test a topical study treatment (called ClearToe Serum®) plus two types of light (red and blue-purple light) in the treatment of chronic venous ulcers.

The ClearToe® liquid is applied to the wound. When the lights shine on the ClearToe®, they trigger a reaction that creates specialized oxygen molecules called Reactive Oxygen Species, or ROS. These ROS disrupt and destroy the biofilm, allowing clearance of the bacteria underneath. The mechanism of applying ClearToe® and activating it with light to destroy biofilm-producing microorganisms has been shown in other clinical contexts, and the ToeFX ClearToe® system is approved for those indications. Its effectiveness in targeting biofilms and bacteria in the treatment of venous leg ulcers has not yet been tested. The ToeFX ClearToe® system is approved by Health Canada for the treatment of onychomycosis (toenail fungus). It has not been approved by Health Canada for the treatment of chronic venous ulcers. Its use in this study is therefore considered investigational.

This pilot study is being done to assess the feasibility and safety of ToeFX therapy in combination with standard of care treatment of chronic venous leg ulcers. Our main objectives are to assess adherence to the one-per-week study treatments, and to note any study device-related, study treatment-related, or serious adverse events, or adverse events that lead to stopping study treatment.

**WHAT WILL HAPPEN DURING THIS STUDY?**

This is an open-label single-arm pilot study. All participants will receive the test treatment as well as standard or care treatment for their chronic venous ulcer.

If you choose to take part in this study, you will participate in the study visits and activities described below.

**Screening Visit**
Study staff will review your medical history to confirm that you are eligible to participate. Eligible participants who provide informed consent will be enrolled in the study.

**Baseline Visit**
The baseline visit will take place during the same appointment as the screening visit. At this visit, the following activities will take place:

Standard of Care Activities
- Medical history
- Review of current medications
- Physical exam
- Wound assessment
- Routine wound cleansing/debridement (as clinically indicated)
- Compression therapy assessment/initiation

Study-Specific Activities
- Demographics
- CEAP classification (Clinical manifestations, Etiology, Anatomic distribution, Pathophysiology)
- Wound photography and wound area measurement
- Wound assessment: Bates-Jensen Wound Assessment Tool (BWAT)
- Pain score (Numeric Rating Scale (NRS) 0-10)
- EQ-5D-5L questionnaire
- ToeFX treatment
- Documentation of study treatment and adherence
- Completion of EQ-5D-5L questionnaire

**ToeFX Treatment**
After your wound has been cleaned and debrided as it normally would, the study doctor will coat your wound with a blue gel (ClearToe® serum) and then allow the gel to soak in for about a minute. A second coat of blue gel may be applied at the study doctor's discretion, allowing it to soak in for about a minute. The study doctor will then place the blue light (ToeFX photodynamic study therapy device) so that the blue light is directed at your wound. The light will be turned on for 5 minutes. The study doctor will then apply wound dressings and compression therapy as usual.

**Study Treatment Visits 2-11**
Subjects will return for Study Treatment Visits once per week for 12 weeks, or until the wound has healed. The following activities will take place at each Study Treatment Visit:
Standard of Care Activities

- Removal of dressing and standard wound assessment
- Routine wound cleansing/debridement (as clinically indicated)
- Application of standard wound dressing
- Assessment and application of compression therapy

Study-Specific Activities

- Review of medical history and adverse events
- Wound imaging and wound-area measurement
- Wound assessment: BWAT
- Pain score (NRS 0-10)
- ToeFX treatment (as described above)
- Documentation of study treatment and adherence

**End-Of-Study Treatment Visit (Visit 12, or at the time of wound healing)**
The End-Of-Study Treatment Visit will be conducted at Visit 12, or earlier if wound healing is observed at an earlier visit.

This visit will include all Study Treatment Visits 2-11 activities, as well as completion of the study-specific Patient Satisfaction Questionnaire and the EQ-5D-5L questionnaire.

**Healing Confirmation Visit (2 weeks after End-Of-Study Treatment Visit)**
If your wound heals during the study treatment window, or by the End-of-Study Treatment Visit, a Healing Confirmation Visit will take place about two weeks later. At this visit, the study doctor will confirm that the wound remains healed, and the following study-specific activities will take place:

- Review of medical history and adverse events
- Wound imaging and wound-area measurement
- Wound assessment: BWAT
- Pain score (NRS 0-10)

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

It is anticipated that about 20 people will participate in this study at a single centre in Toronto. The length of this study for participants is up to 16 weeks. The entire study is expected to take about 9 months to complete and the results should be known in one year.

**WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?**

If you decide to participate in this study you will be asked to do the following:

- Attend and participate in the above listed study visits. The anticipated extra time that the study-specific activities will take at each visit is:
    - Screening Visit: 5 minutes
    - Baseline and Study Treatment Visit 1: 30 minutes
    - Study Treatment Visits 2-11: 20-30 minutes
    - End-of-Study Visit/Study Treatment Visit 12: 30 minutes
    - Healing Confirmation Visit: 10 minutes
- Undergo the study treatment (ToeFX Treatment) in addition to the standard of care wound treatment.

**WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?**

You may experience side effects from participating in this study. Some side effects are known and are listed below, but there may be other side effects that are not expected. If you decide to take part in this study, you should contact the study doctor using the contact information on the first page of this form about any side effects or study-related injuries that you experience.

The reasonably foreseeable risks that you might experience are described below:

- Localized skin reaction: There is a minimal risk of self-limiting, localized skin reaction for participants with allergies to methylene blue or methyl methacrylate.
- Blue dyed skin: There is a chance that the treated skin will remain blue for several days post-study treatment before it fades naturally.
- Discomfort during serum application: There is a moderate risk of discomfort during the application of the ClearToe serum as the brush applicator applies the serum directly onto the wound.
- Discomfort during light treatment: There is a minimal risk of discomfort due to heat on the wound during the application of the blue light.
- There is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:
    - Rash
    - Wheezing and difficulty breathing
    - Dizziness and fainting
    - Swelling around the mouth, throat or eyes
    - A fast pulse
    - Sweating

  Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms.
- Discomfort with questionnaires: You may be uncomfortable answering questions for the patient-reported outcomes questionnaires (EQ-5D-5L, and Patient Satisfaction Questionnaire) since these ask about your experience of your health and your quality of

life. You can choose to skip any question that makes you uncomfortable, or to end the questionnaire at any time.

The effects or discomforts of tests/procedures that are part of this study but are part of your normal clinical care will be reviewed by your treating study doctor, and include the possible discomfort you may experience with wound cleaning, debridement, and compression therapy.

**Unforeseen Risks**
Since the study treatment is investigational, there may be other risks that are unknown.

**Birth Control and Breastfeeding Restrictions**
The effects of the ToeFX treatment on unborn babies or sperm are unknown. You should not take part in this study if you are pregnant or planning pregnancy. If you are able to have children and you are sexually active, it is important that you practice an acceptable method of birth control during this study to prevent pregnancy. Clinically acceptable methods of birth control for this study include intrauterine devices (IUD), birth control pills, hormonal implants, injectable contraceptives, and using barrier methods such as condoms, vaginal diaphragm with spermicide, or sponge.

The safety of the ToeFX treatment during breast-feeding is not known. For this reason, those who are breast-feeding cannot take part in this study.

You will be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

**WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?**

You may or may not benefit directly from participating in this study. Your participation may or may not help other people with venous leg ulcers in the future.

**WHAT OTHER CHOICES ARE THERE?**

You do not have to participate in this study to receive treatment for your chronic venous leg ulcer. If you decide not to participate in this study, you may continue with standard of care wound treatment as usual. The potential benefit of standard of care wound treatment is wound healing. Potential risks include pain, discomfort, and bleeding.

**CAN PARTICIPATION IN THIS STUDY END EARLY?**

The study doctor may decide to remove you from this study without your consent for any of the following reasons:

- The study doctor decides that continuing in this study would be harmful to you.

- You plan to become pregnant, plan to discontinue acceptable birth control, or become pregnant.
- You are unable or unwilling to follow the study procedures.

If you are removed from this study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

You can also choose to end your participation at any time without having to provide a reason. If you choose to withdraw, your choice will not have any effect on your current or future medical treatment or health care.

If you withdraw voluntarily from the study you are encouraged to contact the study team using the contact information on the first page of this form.

If you withdraw your consent, the information about you that was collected before you left the study will still be used. No new information about you will be collected without your permission.

Your data collected during this study may be used for commercial profit (even if identifiers are removed) and you will not share in this profit.

**WHAT ARE THE COSTS OF PARTICIPATING IN THIS STUDY?**

There is no cost to you, your private medical insurance (if any), or the public health insurance plan, for study-specific procedures. The study treatment, study-specific procedures, and study visits will be provided at no charge for the duration of the study. You, the public health insurance plan, or your private medical insurance (if any) will be billed for standard of care procedures.

**WHAT HAPPENS IF I HAVE A RESEARCH RELATED INJURY?**

In case of an injury or illness suffered by participating in this study, you will receive appropriate medical care. The sponsor will cover necessary medical costs not covered by the public health plan or your private medical insurance (if any). By signing this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

**ARE STUDY PARTICIPANTS PAID TO PARTICIPATE IN THIS STUDY?**

You will not be paid to participate in this study. If you decide to participate in this study, you will be reimbursed $25 for each in-person study visit to cover the cost of study related expenses such as transportation or parking. If you attend all 12 Study Treatment Visits the total will be $300, with an additional $25 if you attend a Healing Confirmation Visit. You will receive payment monthly throughout the study. If you do not complete the study for any reason, you will be paid for each study visit you do complete. You may be asked to provide an email address

that can be used to issue payment by email money transfer. This information will be retained and used only for that purpose.

**HOW WILL MY INFORMATION BE KEPT CONFIDENTIAL?**

Your identity will be kept confidential at all times, except where disclosure is required by law. As part of this research, the study doctor will collect the results of your study-related tests and procedures and may also access your personal medical records for health information such as past medical history and test results. Information from this study will be submitted to the sponsor, and to Health Canada and possibly to governmental agencies in other countries (e.g. US Food and Drug Administration) where the study treatment may be considered for approval. Information sent from the study site will contain a study ID, but will not contain your name. The results of this research study may be presented at meetings or in publications but your identity will not be disclosed. Study results will be made available to you upon request once they become available from the sponsor.

To make sure that the health information collected in this study is accurate, it will need to be checked from time to time against your medical records. By signing this form, you authorize direct access to your medical records for the limited purpose of monitoring the study, auditing activities, and reviewing or verifying study data. Some persons may need to see these records in order to monitor the research and verify the accuracy of the study data, including:

- a limited number of representatives from the study sponsoring drug company (namely its monitors and auditors),
- the research ethics review board – Advarra Institutional Review Board (IRB) (an independent ethics committee that reviewed the ethical aspects of this study to help protect the rights and welfare of study participants),
- government regulatory authorities including Health Canada, the US Food and Drug Administration (FDA) and other foreign regulatory agencies.

Your study records including confidential information about you collected during the study will be kept at a secure location and will be collected, used, stored and protected using appropriate administrative, technical, and physical safeguards in accordance with applicable privacy laws and study requirements. Your study records may be stored in Canada or in other countries. If your information is transferred outside of Canada, appropriate safeguards will be in place to protect your information in accordance with applicable privacy laws.

While every effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect your privacy.

By signing this information and consent form, you consent to the collection, access, use and disclosure of your information as described above.

In certain circumstances, researchers may be required by law to disclose information collected during this study (for example, reporting certain communicable diseases, child abuse, or serious risk of harm to yourself or others).

**ARE THERE ANY CONFLICTS OF INTEREST/RELATIONSHIPS?**

There are no conflicts of interest to declare related to this study. The study doctor is receiving financial payment from ToeFX Inc. to cover the cost of conducting this study. The researchers are responsible for conducting this research ethically and in your best interests. If you would like more information about any potential financial or other interests related to this research, please ask the study doctor.

**COMMUNICATION WITH YOUR FAMILY DOCTOR**

With your consent, your family doctor may be informed that you are taking part in this study so that your study doctor and family doctor can help you make informed decisions about your medical care. Please indicate your preference below.

❒YES, I give permission to contact my primary health care provider
❒NO, I do not give permission to contact my primary health care provider

**WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?**

You have the right to ask questions and to receive answers throughout this study.

**WHOM TO CONTACT ABOUT THIS STUDY**

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study such as:

- Whom to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a research participant;
- Eligibility to participate in the study;
- The study doctor's or study site's decision to withdraw you from participation;
- Results of tests and/or procedures;

**Please contact the study doctor at the telephone number listed on the first page of this consent document.**

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, contact:

- By **mail**:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: PRO04244160.

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.

**DOCUMENTATION OF INFORMED CONSENT**

You will be given a copy of this informed consent form after it has been signed and dated by you and the study staff.

Name of Participant: _____

Participant/LAR

By signing this form, I confirm that:

- This research study has been fully explained to me and all of my questions answered to my satisfaction
- I understand the requirements of participating in this research study
- I have been informed of the risks and benefits, if any, of participating in this research study
- I have been informed of any alternatives to participating in this research study
- I have been informed of the rights of research participants
- I have read and understood each page of this form
- I authorize access to my personal health information, medical record and research study data as explained in this form
- I have agreed, or agree to allow the person I am responsible for, to participate in this research study
- I understand that my family doctor may be informed of my participation in this research study

| _____ | _____ | _____ |
|---|---|---|
| Name of participant (print) | Signature | Date |
| _____ | _____ | _____ |
| Name of legally authorized representative (print) | Signature | Date |

_____

Authority of legally authorized representative to act on behalf of participant

**WITNESS DECLARATION** (if applicable)

Was the participant assisted during the consent process (e.g. for needs related to reading ability, visual impairment, motor function deficits, etc.)?

☐ Yes ☐ No

I attest that I was present during the full duration of the informed consent process. The research study appears to have been accurately explained to the participant/LAR and all of their questions have been answered. I confirm that the participant/LAR has provided their voluntary consent to participate.

| _____ | _____ | _____ |
|---|---|---|
| Name of Witness (Print) | Signature | Date |

<u>Person obtaining consent</u>

By signing this form, I confirm that:

- This study and its purpose has been explained to the participant named above
- All questions asked by the participant have been answered
- I will give a copy of this signed and dated document to the participant

| _____ | _____ | _____ |
|---|---|---|
| Name of Person obtaining consent (print) | Signature | Date |