RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	A Randomised Controlled Multicentre Trial, Examining the Effect of Natrox® Oxygen Wound Therapy on the Healing Rate of Chronic Diabetic Foot Ulcers (NOW.T-001)
PROTOCOL NO.:	NOW.T-001 WIRB® Protocol #20191085
SPONSOR:	Inotec AMD Inc
INVESTIGATOR:	Name Address City, State Zip Country
STUDY-RELATED PHONE NUMBER(S):	Name Number(s) (24 hours) [24-hour number is required]

SUMMARY

You are being asked to be in a research study because you are a person with diabetes who has a non-healing wound on your foot (Diabetic Foot Ulcer or DFU). The purpose of this consent form is to help you decide if you want to be in the research study.

You should not join this research study until all your questions are answered, and you understand the answers to those questions.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard medical care (also called Standard of Care, or SOC) is the treatment normally given for a certain condition or illness.
- After reading the consent form and talking with the research staff, you should know which parts of the study are experimental and which are standard medical care.

- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed, then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

PURPOSE OF THE STUDY

The treatment of diabetic foot ulcers (DFUs) continues to be part of the major economic burden of chronic wounds worldwide with costs of at least $50 billion in the U.S. While many DFUs will heal with good standard of care (SOC), the process can take many months. During this time, wounds can become infected and at higher risk for lower extremity amputation. Adding treatments that can speed the healing process will result in lower treatment costs as well as lowering risks of complications.

There is a wealth of evidence to support the benefits of oxygen therapy on wound healing[1-7]. Oxygen is required for all major processes of wound healing and wound hypoxia is common. Skin wounds can receive oxygen from the blood stream via perfusion and from oxygen uptake through the skin. Yet, both wound perfusion and blood oxygen levels are frequently insufficient in patients with chronic wounds due to poor circulation, vascular disruption, and vasoconstriction, thereby reducing the wound's capacity to heal.

The purpose of this study is to find out if adding Natrox® Oxygen Wound Therapy to Standard of Care in chronic Wagner Grade 1 and 2 diabetic foot ulcers (DFUs) makes those wounds heal faster than when they are treated with SOC alone.

PROCEDURES

You will sign and date this informed consent form before the study doctor does any study-related procedures. Once the informed consent is signed, the 2-week long Screening Period starts. The purpose of the Screening Period is to make sure you meet all the requirements to be in the study. The Screening Period for this study has 2 visits, each one week apart.

If your wound is on the bottom of your foot a cast will be used to offload (take pressure off) the wound. The cast will be changed 7 days later at your second screening visit. This type of cast is called a Total Contact Cast (TCC). If you have never worn a TCC before you will have an extra visit 3 days after your first screening visit for a cast change and to make sure you're not having problems with it. After the screening period, the TCC will be changed weekly at your scheduled treatment visit.

During the **Screening Period,** the study doctor will perform the following assessments and procedures:

- Demographics such as age, sex and race
- Medical and surgical history, including foot ulcer history and any other wounds
- Find out what medications you take and if you have any changes
- Physical examination, including vital signs
- Check how much pain you're having from the study ulcer
- Study ulcer history and assessment e.g. how long you've had the wound, how much drainage and what type of drainage
- Check for infection in the study wound
- Measure the blood-flow to your foot by getting an ABI (Ankle-Brachial Index), SPP (skin perfusion pressure), TCOM (transcutaneous oximetry) measurement, TBI (Toe-Brachial Index) or Arterial Doppler Study if you don't have test results within the past 90 days
- Test your HbA1c with a fingerstick if you don't have test results within the past 90 days
- Pregnancy test (blood or urine) if you are a female of childbearing potential
- Debride (remove dead, damaged or infected tissue) the study ulcer, if necessary
- Clean the study ulcer
- Take a digital photograph and measurement of the study ulcer
- Place SOC dressings on your wound (absorbent dressings of hydrofiber/alginate)
- Offload (take pressure off the wound) with a TCC, if the wound is on the bottom of your foot
- Check that you've been wearing the cast correctly and not having any problems with it, (if applicable)
- Review your eligibility to continue in the screening period
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If you successfully complete the Screening Period, you will immediately move to the Treatment Period which has 13 scheduled visits.

At Treatment Visit 1, the study doctor will perform the following assessments and procedures:

- Check how much pain you're having from the study ulcer
- Check that you're wearing the TCC correctly and not having any problems with it, (if applicable)
- Check for any changes in your health
- Check for any changes in your medications or treatments
- Assess the study ulcer, e.g. how much drainage and what type of drainage
- Check for infection in the study wound
- Clean the study ulcer
- Debride the study ulcer, (if necessary)
- Take a digital photograph and measurement of the study ulcer
- Measure the change in wound size over the past 2 and 4 weeks
- Confirm you meet all the requirements to continue in the study
- Randomization

- For Group 1: Placement of SOC dressings (absorbent dressings of hydrofiber/alginate) and Natrox® Oxygen Wound Therapy
- For Group 2: Placement of SOC dressings (absorbent dressings of hydrofiber/alginate) only
- Offload (take pressure off the wound) with a TCC if the wound is on the bottom of your foot

If, after reviewing the information from the screening period the study doctor finds that you do not meet all the requirements to continue in the study, you will be finished with the trial.

If the study doctor finds that you do meet all requirements to be in the study, you will be randomized to one of two treatment groups:

- Group 1 will receive standard of care therapy and Natrox® Oxygen Wound Therapy.
- Group 2 will receive standard of care therapy alone.

Randomization is like flipping a coin: you have an equal chance of being placed in either group. Neither you, your study doctor, nor the research staff can choose the group you will be in. Your study doctor has a sealed envelope assigned to your study number that contains a letter saying which study group you will be in. You must be okay with being in either group.

The study doctor will apply the treatment that you are randomized to and make sure offloading of your wound (if applicable) is satisfactory. You will then be seen once a week up to 12 more weeks for additional treatment visits.

At weekly Treatment Visits 2-12, the study doctor will perform the following assessments:

- Check how much pain you're having from the study ulcer
- Check that you've been wearing the TCC correctly and not having any problems with it, (if applicable)
- Check for any changes in your medications or treatments
- Check for any changes in your health
- Check if the study ulcer is fully healed
    - If the study ulcer is 100% healed, you will be finished with the trial
- Assess the study ulcer, e.g. how much drainage and type of drainage
- Check for infection in the study wound
- Clean the study ulcer
- Debride the study ulcer, if necessary
- Take a digital photo and measurements of the study ulcer
- For Group 1: Placement of SOC dressings (absorbent dressings of hydrofiber/alginate) and Natrox® Oxygen Wound Therapy
- For Group 2: Placement of SOC dressings (absorbent dressings of hydrofiber/alginate) alone
- Offload (take pressure off the wound) with a TCC if the wound is on the bottom of your foot

At **Visit 13 (End of Study Visit)**, or at any earlier visit if you heal before Visit 13, the study doctor will perform the following assessments:

- Check how much pain you're having from the study ulcer, if not fully healed
- Check that you've been wearing the TCC correctly and not having any problems with it, (if applicable)
- Check for any changes in your medications or treatments
- Check for any changes in your health
- Check if the study ulcer is fully healed
    - If the study ulcer is 100% healed, you will be finished with the trial
- If not fully healed, assess the study ulcer e.g. how much drainage and what type of drainage
- Check for infection in the study wound, if not fully healed
- Clean the study ulcer, if not fully healed
- Debride the study ulcer, if not fully healed, and if necessary
- Take a digital photograph of the healed area, or a digital photograph and measurement of the study ulcer if not fully healed
- Place a standard medical dressing on the study ulcer, if not fully healed
- Complete the Study Exit Form

There may be times your study doctor will want you to come in for an **Unscheduled Visit;** for example, you have a lot of drainage and they want to change the dressings more than once every week.

At an **Unscheduled Visit** the study doctor will perform the following assessments:

- Check how much pain you're having from the study ulcer
- Check that you've been wearing the TCC correctly and not having any problems with it
- Check for any changes in your medications or treatments
- Check for any changes in your health
- Debride the study ulcer, if necessary
- For Group 1: Placement of SOC dressings (absorbent dressings of hydrofiber/alginate) and Natrox® Oxygen Wound Therapy
- For Group 2: Placement of SOC dressings (absorbent dressings of hydrofiber/alginate) alone
- Offload (take pressure off the wound) with a TCC if the wound is on the bottom of your foot

RISKS AND DISCOMFORTS

The possible risks or discomforts associated with receiving the Natrox® Oxygen device may include potential allergic reaction/ skin irritation. To decrease the already unlikely chance of allergic reaction the device is made of medical grade materials.

The possible risks associated with debridement (standard of care) include allergic reaction to anesthetic and/or antibiotics, pain, infection and maceration.

There may be side effects that are not known at this time.

Women who are pregnant or nursing a child may not take part in this study.

Before entering the study, you and your study doctor must agree on the method of birth control you will use during the entire study.

If you think that you have gotten pregnant during the study, you must tell your study doctor immediately. Pregnant women will be taken out of the study; however, the pregnancy will be followed to outcome for safety follow up.

Other Risks

Your diabetic foot ulcer may stay the same or may get worse during this study.

NEW INFORMATION

You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

Your diabetic foot ulcer may get better or heal while you are in this study; however, improvement or healing cannot be promised. The results of this study may help people with diabetic foot ulcers in the future.

COSTS

Inotec AMD Inc, will provide the Natrox® Oxygen Wound Therapy device free of charge during this study. Tests and procedures that are done only for the study will not be billed to you or your insurance company.

You or your insurance company may be billed for:

- Any standard medical care given during this research study.

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

PAYMENT FOR PARTICIPATION

You will receive a $100.00 stipend for each completed study visit to help pay for your travel and expenses.

At the end of your first Screening Visit you will receive a reloadable gift/debit card to use throughout the study. Payment will be added onto this card within 24-48 hours of the end of each completed study visit. If you do not finish the study, you will be paid only for the visits you have completed.

ALTERNATIVE TREATMENT

If you decide not to enter this study, there are other choices available. These include receiving standard of care (cleaning the wound, reducing pressure on the wound, using bandages to keep the right amount of moisture in the wound, debridement, and, if necessary, antibiotics,) and/or receiving other treatments that may be available in your clinic. Ask the study doctor to discuss these alternatives with you. You do not need to be in this study to receive treatment for your condition, including receipt of therapy with the study device outside of this research.

COMPENSATION FOR INJURY

If you are injured or get sick as a result of being in this study, call the study doctor immediately. The study doctor will provide emergency medical treatment or direct you where to go for emergency medical treatment. Your insurance will be billed for this treatment. The sponsor will pay any charges that your insurance does not cover. No other payment is routinely available from the study doctor or sponsor.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate, or you may stop participating in the study at any time. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled.

You can be taken out of this study at any time by the study doctor or the sponsor without your consent for any reason, including:

- If it is in your best interest
- If you do not consent to continue in the study after being told of changes in the research that may affect you
- If you are significantly non-compliant with the requirements of the protocol.
- If you become pregnant (Note: the pregnancy will be followed up to term for safety follow-up. Relevant safety information collected after the study has completed will be reported as supplemental information.)
- If you have surgery to improve the blood flow on the lower leg that the study ulcer is on.

- If your ulcer gets worse to the point where there is exposed bone.
- If your study ulcer merges with another ulcer.
- If you are treated with a medication that's not allowed.

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you leave the study safely.

SOURCE OF FUNDING FOR THE STUDY

The sponsor, Inotec AMD Inc, will pay for this research study.

CONFIDENTIALITY

Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies that are contracted by the sponsor to have access to the research information during and after the study.

The information may also be given to the U.S. Food and Drug Administration (FDA). It may be given to similar governmental agencies in other countries. Medical records which identify you and the consent form signed by you may also be looked at and/or copied for research or regulatory purposes by:

1. Department of Health and Human Services (DHHS) agencies,
2. the institution where the research is being done, and
3. Western Institutional Review Board® (WIRB®).

Whenever possible, your identifying information will be protected; for example, a study number will be used instead of your name. Complete confidentiality cannot be guaranteed because of the need to give information that identifies you to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be used in those presentations.

QUESTIONS

Contact [Name] at [Number] (24 Hours) for any of the following reasons:

- if you have any questions about your participation in this study,
- if you feel you have had a research-related injury or a reaction to the study drug, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and you understand the answers to those questions.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

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.

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

I authorize the release of my medical and research records for the purpose of this study.

By signing this consent form, I have not given up any of my legal rights.

CONSENT SIGNATURES:

_____
Subject Name (printed)

_____ _____
Signature of Subject Date

_____ _____
Printed Name of Person Conducting the Informed Consent Discussion Position

_____ _____
Signature of Person Conducting the Informed Consent Discussion Date

****For Sites in California****

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.

Who may use and give out information about you?
The study doctor and the study staff. [They may also share the research information with [enter SMO company name], an agent for the study doctor. delete if the site does not have an SMO]

Who might get this information?
The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- The institution where the research is being done,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to make sure that the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
This permission will be good until December 31, 2060.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Authorization:
I have been given the information about the use and disclosure of my health information for this research study. My questions have been answered.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

AUTHORIZATION SIGNATURE:

Signature of Subject	**Date**