**INDIANA UNIVERSITY INFORMED CONSENT STATEMENT AND AUTHORIZATION FOR RESEARCH**

**TITLE:** Diabetic Foot Ulcer (DFU) Biofilm Infection and Recurrence

**PROTOCOL NO.:** 2007806775
WCG IRB Protocol #20202555
2007806775

**SPONSOR:** Indiana University

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**STUDY-RELATED PHONE NUMBER(S):** 317-278-2736
317-944-5000; ask for Dr. Sen to be paged

## ABOUT THIS RESEARCH

You are being asked to participate in a research study. Scientists do research to answer important questions which might help change or improve the way we do things in the future.

This consent and authorization form will give you information about this study to help you decide whether you would like to participate. It is your choice whether you want to be in this research study. Please read this form, and ask any questions you have, before agreeing to be in this study.

## STUDY SUMMARY

Diabetic foot ulcers (DFU) are one of the most common reasons for the hospitalization of diabetic patients and frequently results in amputation of lower limbs. Of the one million people who undergo non-traumatic leg amputations annually worldwide, 75% are performed on people who have type 2 diabetes. The rate of amputation in patients with DFU is 38.4%. Infection is a common (greater than 50%) complication of DFU**.** Biofilms are estimated to account for 60% of chronic wound

infections. A biofilm can occur if a chronic infection causes bacteria to grow in a slime enclosed group. This grouping of bacteria is called a biofilm. Standard clinical tests to detect infection may not detect biofilm infection. Thus, biofilm infection may be viewed as a silent threat in wound care.

Our pre-clinical large animal work demonstrates that wounds with a history of biofilm infection may meet the standard criteria for wound closure, but the repaired wound-site skin is deficient in barrier function. This has led to the concept of "functional wound closure," where the current clinical definition of wound closure is supplemented with a functional parameter – restoration of skin barrier function as measured by how much water loss through the skin can be detected.

In this study, we hope to determine how biofilm infection disrupts the healing of diabetic foot ulcers. We also hope to determine if a diabetic foot ulcer that is closed but has a deficient skin barrier has a higher rate of recurring than closed diabetic foot ulcers with an appropriate skin barrier.

This study will investigate the significance of using Trans Epidermal Water Loss (TEWL) measurements with the DermaLab probe as a way to predict diabetic foot ulcer healing.

If you choose to participate in this research, your participation is expected to last about 30 weeks. This research does not involve any treatment and you may not gain personal benefit from joining the study, but you may provide valuable information that can help others in the future. There may be risks from participating in the research such as discomfort from some of the procedures including punch biopsies where a small piece of the skin and wound is sampled, local anesthetic numbing medications, and tests to measure the blood flow to the area of your wounds. See below for additional details. Your alternative is to not participate in this study.

**Please review the rest of this document for more details about this study and the things you should know before deciding whether you want to participate.**

**Why is this study being done?**
The purpose of this study is to determine the role that biofilm infection plays in diabetic foot ulcer healing and recurrence.

**WHO IS CONDUCTING THIS STUDY?**
The study is being conducted by Dr. Chandan Sen of the IU Center for Regenerative Medicine and Engineering at the Indiana University School of Medicine. It is funded by a grant from the National Institutes of Health and the IU Center for Regenerative Medicine and Engineering.

**HOW MANY PEOPLE WILL TAKE PART?**
If you agree to participate, you will be one of up to 405 subjects nationally to participate in this study. You were selected as a possible participant because you have a diabetic foot ulcer. There will be about 115 patients recruited from Aiyan Diabetes Center and about 90 from Indiana University.

**WHAT WILL HAPPEN DURING THE STUDY?**
If you agree to be in the study, you will complete the following activities:

This study takes part in 2 phases as described below. Participants will be followed for 16 weeks for wound closure (*Phase A*). Following this, participants may begin *Phase B* (refer to study procedures below) dependent upon wound closure. At this time, the wounds will be subject to Standard of Care (SoC) procedures followed by all wound clinicians.

**Phase A:**

Study Visit 1 (pre-closure enrollment)
This initial visit will take place following completion of your regularly scheduled wound care clinic visit and the following activities will take place:

- Informed consent will be obtained
- Baseline demographics, medical history, and current medications will be recorded such as:
- Age, gender, race/ethnicity, smoking status, transcutaneous oxygen measurement, TBI,
- Nutritional status will be recorded as documented by albumin levels and chart records.
- Wound data (etiology, size, location, duration, wound care modality) will be recorded
- Previous wound treatment for the past 30 days, as well as the total number of debridement's since wound onset
- Wound swab for culture and wound infection history
- Baseline labs, including Hemoglobin A1c will be drawn; only labs drawn as standard of care since the onset of your current wound will be collected.
- You will be asked to complete the Health survey, pain scale and Cardiff wound impact questionnaire
- Wound Site evaluation including transcutaneous oximetry (TcOM)/toe brachial index (TBI)/ankle brachial index (ABI) will be completed for wounds below the knee if not already completed per standard of care within the previous 12 months prior to enrollment. The TcOM/TBI/ankle brachial index (ABI) procedures are described below in the risk section of this document.

- Hemoglobin A1c finger stick will be done if you do not have an A1c available as standard of care in your medical record within 90 days prior to enrollment. Hemoglobin A1c point of care testing will be drawn for diabetic subjects who do not have an A1c available as standard of care in their medical record within 3 months prior to enrollment to confirm study eligibility. An A1c greater than 12 will exclude you from the study and no further study activities will be completed.
- Wound edge tissue specimen collection. Debrided tissue will be obtained by the subject's physician if available. 2 punch biopsies will also be performed.
    - *Debridement and biopsy collection:* Wound edge tissue will be collected though either 3mm punch biopsy or sharp debridement as part of this study .Debrided tissue will be collected for this study. In brief, tissue from wound edge will be collected through though either 3mm punch biopsy or sharp debridement as part of this study until appearance of blood. Samples will be used to determine whether

the wound is infected using electron microscopy and quantitative bacterial cultures. The wound tissue will be collected by an approved study team member, all of whom are trained providers.

- *For the debridement collection*, the wound bed will be prepared with local anesthetics as appropriate. This is not standard because some patients will not have feeling in the area of the wound. A sharp surgical tool will be used to obtain wound tissue specimen. The sample will be rinsed with normal saline and patted dry with Kimwipe, then embedded in OCT and immediately snap frozen in liquid nitrogen (LCM) or stored in specific buffer for scanning electron microscopy. Samples collected at the University of Arizona or Aiyan will be shipped to IU for blinded processing and analyses.
- For subjects who are not appropriate for debrided tissue, a swab will be collected to send for culture.
- After debridement (if needed), the clinician may collect two tissue samples from the wound edge using a punch biopsy device. The biopsy device will look like a hollow pen, approximately 3 mm or 1/8 of an inch wide at the tip and is pressed into the skin to snip a piece of tissue. This piece of tissue is half the size of a pencil eraser in width and the length of a grain of rice. It is normal to feel twisting or pressure during this procedure but not pain. Prior to beginning, the area will be numbed with a local anesthetic such as lidocaine.

- The medical records from standard of care wound care visits will be reviewed and followed for up to 16 weeks or until your wound has closed, whichever comes first. The research staff will also call you as needed if the wound is noted to be healed.

**Study Visit 2 (post-closure, Week 0):** You will return to the clinic within 10 days of wound closure or at 16 weeks (plus/minus 2 weeks) if your wound has not healed. The wound closure evaluation will be per standard of care. If your wound has not healed, your participation in the study will end but the following information will be collected:

  - Wound data (etiology, size, location, duration, wound care modality, determination of presence of callus) will be recorded
  - A digital photograph of the wound will be taken.
  - Quality of Life questionnaire SF-12 Health survey, Visual Analogue Pain scale, and Cardiff wound impact questionnaire.
- If the wound has been determined to be visually healed at or prior to this visit, TEWL measurements will be taken and you will be asked to continue in this study.

- For Transepidermal water loss (TEWL) measurements: The DermaLab probe will be placed on the skin. The measurement takes between 7-20 seconds. The measurement time is automatically controlled and shown on the display. There will be 5 measurements obtained over the healed wound site, at 12, 3, 6, and 9 o'clock around the wound edge, as well as one in the middle. A reference (control) TEWL measurement will be taken from intact skin at an anatomically matched site on the opposite side of your body.
  - TEWL measurements will be measured using a pen like device from the DermaLab TEWL probe by touching the wound five times (30 seconds each time) at different locations.

These TEWL measurements will also be made on unwounded skin at five different locations (about 30 seconds each location).

- Various laboratory tests that have been drawn per standard of care since enrollment will be recorded from your medical records into your research study file.
- A review of your medications and any problems you are having will be completed.
- If the wound has been determined to be visually healed at or prior to this visit, you will continue to Phase B of the study which is described below.

**Phase B**

**Study Visits 3-4 (post-closure Week 2 and Week 12)**:

You will return to the clinic following wound closure for follow up evaluation of the healed wound over 12 weeks. The visits will be at 2 and 12 weeks (+/-2 weeks) after visit 2. These visits will last about 1 hour. You will be asked to refrain from using any topical product(s) (lotion, ointments, etc.) the day of the study visits.

- Digital photos of the wound site will be taken.
- Wound site evaluation for signs of recurrence and callus determination, including the date of wound healing will be obtained. You will receive weekly phone calls for wound site evaluation
  - TEWL measurements will be obtained from the DermaLab TEWL probe as described above.
  - Medication review and adverse event review will be completed
    - Various labs that have been drawn per Standard of Care since enrollment, medication review, and any adverse events will be recorded.
    - You will be asked to complete a quality of life survey (SF-12 Health survey, Visual Analogue Pain scale, Cardiff wound impact questionnaire and diabetic foot scale questionnaire) at the final study visit (at wound recurrence or week 12). You will complete quality of life surveys at the final study visit (at wound recurrence or week 12).

**NOTE:** If the wound recurs (reopens) at any point during the 12-week study follow-up, you will be asked to notify the research staff and return as soon as possible for a FINAL study visit. TEWL measurements and all other study activities will take place as scheduled. This visit will conclude the study participation and no further follow-up will be required. **We do not plan to share the results of any of the research activities with you.**

**WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?**

The risks, side effects, and/or discomforts of participating in this study include:

*This is not a treatment study. There is NO medical intervention or any invasive approaches planned as part of this study.*

***Trans Epidermal Water Loss*** **TEWL measurements** are noninvasive measurements (meaning they are external measurements and do not pierce your skin) and expected to cause minimal discomfort. This will be measured using a pen like device touching the wound five times (30 seconds each time) at different locations.

**Hemoglobin A1c:** Risks involved with this testing are minimal and include minor discomfort and bleeding. The finger that will be pricked will be cleaned with an alcohol wipe prior to being pricked, and will be covered with a Band-Aid after testing.

**Tissue Debridement:** The risks are pain, bleeding, infection, and delayed wound healing.

**Ankle Brachial Index:** The ABI test is non-invasive and may result in temporary discomfort around the ankle or foot when the cuff is inflated, but does not present any further physical or medical risks. If the inflation of the cuff becomes extremely painful to you, you can ask us to stop the procedure.

**Transcutaneous Oximetry (TCOM)**
Transcutaneous oximetry (TCOM) is a noninvasive test that directly measures the oxygen level of tissue beneath the skin. Because oxygen is carried to tissues by blood flow in the arteries, TCOM is an indirect measure of blood flow. This test is often used to evaluate advanced peripheral arterial disease, a condition in which blood flow to an extremity (usually the leg) is greatly reduced. The test is performed in a vascular diagnostic laboratory and causes no discomfort. The area to be tested is first cleaned with alcohol and cleared of any wound dressings. If necessary, the site is also shaved. A gel that conducts electrical impulses is applied, and then the physician places adhesive sensors containing a platinum electrode that can sense oxygen on the affected limb.

Electrodes in the sensors heat the area underneath the skin to dilate (widen) the capillaries so oxygen can flow freely to the skin, providing an optimal reading. This takes about 15 minutes. The readings are converted to an electrical current and the signal is displayed on a monitor and recorded. Once the test is completed, the sensors are removed, the testing sites are cleaned, and any dressings are reapplied.

Transcutaneous oximetry has no known side effects or complications and is essentially risk free.

**Toe Brachial Index (TBI)**
TBI is a noninvasive test that directly measures the severity of peripheral arterial disease present in a lower extremity. The test is performed using a blood pressure cuff that is fitted around a toe and arm. The measurement is generated using the systolic blood pressure readings from the arm and toe. The TBI test may result in temporary discomfort around the toe or arm when the cuff is inflated, but does not present any further physical or medical risks.

**Punch Biopsy**
Diabetic Foot Ulcer (DFU) tissue biopsies are sometimes done as part of standard of care assessment. Known risks from tissue collection include pain, bleeding, infection, wound expansion, and scar. These are the same risks associated with standard of care wound debridement and the ulcer itself, so these risks, as associated with being in the study, are only slightly higher. To help reduce these risks, procedures will only be performed within the clinic by trained healthcare providers. Local anesthetic

will be used to lower the risk of pain. Sterile instruments and techniques will be used to lower the risk of infection.

**Local Anesthesia**
Local anesthesia can cause temporary discomfort, allergic reaction, bruising or bleeding.

**Questionnaires:** Some of the questions may make you uncomfortable. You do not have to answer any questions that make you uncomfortable.

**Confidentiality**: Loss of confidentiality is a potential risk, but we will make every effort to keep your study data secure.

**For Women of Childbearing Potential:**
We are unsure of the risks to a fetus and cannot enroll women who are pregnant or planning to become pregnant. If you are a female of child-bearing potential please attest below that you are currently not pregnant or planning to become pregnant and the date of your last menstrual period.

_____ I am currently not pregnant and not planning to become pregnant
Date of last menstrual period (MM/DD/YYYY) _____

This study may have some side effects which are unknown at this time.

**WHO WILL PAY FOR MY TREATMENT IF I AM INJURED?**
If you are injured as a result of participating in this study, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. No money or funds are set aside to pay for these types of injuries. You are not giving up any legal rights or benefits to which you would otherwise be entitled to by signing this Informed Consent form. If you are injured as a result of this study, you do not give up your right to pursue a claim through the legal system.

**WHAT ARE THE BENEFITS OF TAKING PART IN THE STUDY?**
We don't expect you to receive any personal benefit from taking part in this study, but we hope to learn things that will benefit people and help scientists in the future.

**WHAT ARE MY ALTERNATIVES TO PARTICIPATING IN THIS STUDY?**
**This is not a treatment study. Your alternative is not to participate.** You will still receive standard of care treatment for your diabetic foot ulcer outside this study.

**WILL I BE PAID FOR PARTICIPATION?**
You will be paid $50 for Study Visit 1, and $50 for completion of Study Visit 2. Study Visits 3 and 4 will be paid at $50 for each visit completed at the clinic. Compensation will only be given for completed visits.

If you receive $600 or more in one calendar year from Indiana University, you will be required to provide your Social Security number or tax identification number to Indiana University. You will receive a 1099 tax form the following January and will need to report this payment as income on your federal and state tax returns. You are responsible for paying any state, federal, or Social Security taxes. If you have questions regarding how this impacts your tax return, please contact a tax professional to assist you. If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Indiana University to deduct 30% from your compensation to pay required taxes on your behalf.

**HOW WILL MY INFORMATION BE PROTECTED?**

Every effort will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. No information which could identify you will be shared in publications about this study.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees and the WCG Institutional Review Board (WCG IRB), and any state or federal agencies who may need to access your medical and/or research records (as allowed by law). State and federal agencies may include the Office for Human Research Protections (OHRP) for federally-funded research and the US Food and Drug Administration.

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.

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

For the protection of your privacy, this research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use any information, documents, or specimens that could identify you in any legal action or lawsuit unless you say it is okay.

However, there are some types of sharing the Certificate does not apply to. The Certificate does not stop reporting required by federal, state, or local laws, such as reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate does not stop a government agency who is funding research from checking records or evaluating programs. The Certificate also does not prevent your information from being used for other research when allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may still give them permission to release information to insurers, medical providers, or others not connected with the research

**HOW WILL MY INFORMATION AND SPECIMENS BE USED FOR RESEARCH IN THE FUTURE?**
Information or specimens collected from you for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify you will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent. We will not use the specimens collected as a part of this study for whole genome sequencing, which involves mapping all of your DNA. Only the bacterial genome of your wound will be tested.

Specimens collected from you for this research may be used to develop products which could be sold in the future. The investigator does not plan to share any profits or losses from the sale of those products with you.

The information released and used for this research will include:

- Hospital discharge summary
- Medical history/treatment
- Medications
- Mental Health records
- Consultations
- Radiology films (like X-rays or CT scans)
- Laboratory/diagnostic tests
- Psychological testing
- Pathology reports
- Operative reports (about an operation)
- Pathology specimen(s) and/or slide(s)
- Diagnostic imaging reports

If you agree to participate, you authorize the following to disclose your medical record information:

- Indiana University Health
- Indiana University Health Physicians
- IUMG – Primary Care Physicians
- Eskenazi Health
- Aiyan Diabetes Center
- Indiana Network for Patient Care (INPC)

The following individuals and organizations may receive or use your identifiable health information:

- The researchers and research staff conducting the study
- The Institutional Review Boards (IRB) or its designees that review this study
- Indiana University
- Aiyan Diabetes Center
- US or foreign governments or agencies as required by law
- Data safety monitoring boards and others authorized to monitor the conduct of the study
- The following research sponsors: Indiana University
- State or Federal agencies with research oversight responsibilities, including but not limited to:
    - Office for Human Research Protections (OHRP)
    - National Institutes of Health (NIH)

Information and specimens collected for this study may be used for other research studies or shared with other researchers for future research. If this happens, information that could identify you, such as your name and other identifiers, will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

**WILL IT COST ME ANYTHING TO PARTICIPATE?**
There is no cost to you for taking part in this study. Any visits, treatments or procedures done as standard of care will be billed to your or your insurance company in the usual manner.

You may choose to request transportation for any research visit. The research staff will arrange this at no cost to you.

**WHO SHOULD I CALL WITH QUESTIONS OR PROBLEMS?**
For questions, concerns, or complaints about the study or a research-related injury, contact the researcher, Dr. Chandan Sen, at 317-278-2736. If you cannot reach the researcher during regular business hours (i.e., 8 a.m. to 5 p.m.), please call the IU Human Subjects Office at 800-696-2949 or at irb@iu.edu. After business hours, please call 317-944-5000 and ask for Dr. Sen to be paged.

For questions about your rights as a research participant, to discuss problems, complaints, or concerns about a research study, or to obtain information or to offer input, please contact the IU Human Subjects Office at 800-696-2949 or at irb@iu.edu.

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at (855) 818-2289, researchquestions@wcgirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

**WHAT IF I DO NOT PARTICIPATE OR CHANGE MY MIND?**
After reviewing this form and having your questions answered, you may decide to sign this form. Or, you may choose not to participate in the study. This decision is up to you. If you choose not to participate in this study or change your mind after signing this document, it will not affect your usual medical care or treatment or relationship with IU Health or Aiyan Diabetes Center. As participation in this study is voluntary, deciding to withdraw to choosing not to participate will not result in any penalty or loss of benefits to which you are otherwise entitled.

If you change your mind and decide to leave the study in the future, the study team will help you withdraw from the study safely. If you decide to withdraw, you can just tell any member of the study team that you wish to withdraw. If you choose to withdraw your authorization for use and disclosure of your protected health information, you must do so in writing by notifying Chandan K Sen 975 W. Walnut Street, Suite 454, Indianapolis, Indiana 46202. If you withdraw your authorization, you will not be able to continue in this study. However, even if you cancel this authorization, the research team, research sponsor(s), and/or the research organizations may still use information about you that was collected as part of the research project between the date you signed this document and the date you cancelled this authorization. This is to protect the quality of the research results. Otherwise, this authorization remains valid until the research ends and required monitoring of the study has been completed.

The researchers may stop your participation in the study even if you do not want to stop if you do not return to the wound center on a regular basis and therefore no information from your standard of care visits could be obtained for this study.

**PARTICIPANT'S CONSENT AND AUTHORIZATION**

In consideration of all of the above, I agree to participate in this research study. I will be given a copy of this document to keep for my records.

_____

Participant's Printed Name Date

_____

Participant's Signature

_____

Participant's Address

_____ _____

Printed name of Person Obtaining Consent Date

_____

Signature of Person Obtaining Consent