Protocol ID: MDX-DEB-001
Brief Title: Debritom - Micro Water Jet Technology and Wound Healing
Date: September 30, 2019

RESEARCH PROPOSAL

Evaluation of Micro Water Jet Technology and the Progression of Wound Healing:

A Prospective Cohort Evaluating the Efficacy of Micro Water Jet Technology in the debridement and healing of Chronic Lower Extremity Ulcers

PROTOCOL SUMMARY

Study Title
Evaluation of Micro Water Jet Technology and the Progression of Wound Healing: A Prospective Cohort Evaluating the Clinical Efficacy of Micro Water Jet Technology in the debridement and healing of Chronic Lower Extremity Ulcers.

Indication
This study will investigate the clinical efficacy of micro water jet technology in the debridement and healing of chronic lower extremity ulcers.

Objectives
The primary objective of the study is to assess the clinical efficacy of micro water jet technology in the debridement and healing of chronic lower extremity ulcers in terms of wound size, depth/extent, and percent wound reduction and healing. Additional assessments will include evaluating changes in leg rest pain score using a visual analogue scale (VAS); incidence of infection, and pain during debridement via the VAS scale as well as patient feedback regarding their debridement experience with micro water jet technology. The exploratory objective is to use near-infrared images of the wound (taken $Snapshot_{NIR}$, a specialized near-infrared camera) for the characterization and measurement of tissue oxygenation that could enable correlation of wound tissue oxygenation before and after debridement with micro water jet technology.

Study Design
This is a prospective cohort, single-center, open-label study in subjects with chronic lower extremity wounds. The study will enroll up to 20 subjects. Subjects will undergo screening evaluations to determine eligibility to enroll in the study. All study subjects will receive micro water jet technology debridement as opposed to other debridement methods as part of their wound care treatment. The other aspects of subjects wound care protocol will remain unchanged. In the case of bilateral limb ulcers, or multiple ulcers, subjects will have the option to receive micro water jet debridement on one or all of the ulcers.

Study Population
Patients, male or female age 18 or older, with uninfected, chronic lower extremity ulcers greater than one-month duration that has not adequately responded to conventional ulcer therapy

Length of Study
Up to 20 weeks, sooner pending wound healing as defined by 100% re-epithelialization.

Study Treatments
All study subjects will receive micro water jet technology debridement as opposed to traditional debridement using instruments or other means of debridement. Other aspects of subjects wound care protocol will remain unchanged.

Overview of Efficacy Assessments
The following efficacy assessments will be performed:

1. The extent and size of ulcers (summation of the products of the long x short axis for all ulcers measured in centimeters squared, plus ulcer depth) will be evaluated and photographs of ulcers taken during screening and on all clinic visits up to 20 weeks or when the ulcer is healed, whichever is sooner.
2. Leg rest pain score – VAS graded from 0 (pain free) to Grade 10 (maximum pain) during screening on again on all clinical visits for up to 20 weeks, sooner pending wound healing.
3. Pain during Debridement score – VAS graded from 0 (pain free) to Grade 10 (maximum pain) during on all clinical visits when debridement is performed for up to 20 weeks, sooner pending wound healing.
4. Subjects feedback regarding their debridement experience with micro water jet technology will be collected on all clinical visits when debridement is performed.
5. Incidence of wound infection.

The following exploratory assessments may be performed pending availability of near-infrared image camera:

1. Near-infrared image of the wound before and after debridement.

Data and Safety Monitoring Plan

We plan to use the NIDDK 'Data & Safety Monitoring (DSM) Guidelines for Clinical Trials'. The PI will evaluate the data on an ongoing basis and quarterly reports will be prepared to evaluate the progress of the trial (accuracy of data, verifying consent of subjects, and adherence to protocol schedule.). Clinical and patient data will be maintained, segregated and secured in locked filing cabinets only accessible to the Investigators. Patient records will be held as strictly confidential and names, or other identification, will not be used for publication or other purposes. All employees related to this proposal will be certified in accord with the NIH Human Participants Protection Education for Research Teams.

Sample Size Estimation:

Previous work done suggests that a small case series of 16 patients is adequate as a pilot trial. Accounting for a 20% potential fall out rate means that a total of 20 subjects should be enrolled into the study.

Data Analysis

Data analysis will include descriptive statistics and Chi-square and Fisher's exact tests for categorical variables. Continuous variable will be assessed using the Student t test, and where possible linear regression models. Outcomes variables will be compared with repeated measures of analysis of variance tests. Statistical significance will be accepted for p values $<.05$.

TABLE OF CONTENTS

1. INTRODUCTION

Chronic ulcerations are wounds that have failed to properly proceed through the repair process and do not produce functional or anatomic integrity within a three month healing period.[1] The underlying causes of chronic wounds often include venous insufficiency, arterial perfusion, diabetes, unrelieved pressure as well as contributing systemic factors such as immunosuppression, nutrition and infection. Due to a population of increasing age and weight, and the comorbidities of diabetes and venous insufficiency, lower extremity ulcers that are vascular and/or diabetic in nature are the most frequently encountered chronic wounds.[1,2] The prolonged healing process of chronic ulcerations results in both economic loss and an impaired quality of life for patients that suffer from such wounds. Not only does the management of chronic wounds drain healthcare resources, but failure to manage could lead to even more devastating situations such as sepsis and amputation.[3, 4]

Debridement is the removal of devitalized or necrotic tissue or foreign bodies from a wound[5] and is considered by many as the key initial first step in wound healing. Debridement may aid wound healing by removing tissue with the highest bacterial counts, thereby bringing the wound into bacterial balance. Debridement can also activate platelets to release the contents of their alpha granules. The released growth factors stimulate the inflammatory response that is believed to play an important role in wound healing. Optimum debridement should achieve a balance between the removal of necrotic tissue and preservation of healthy tissue and not inhibit subsequent healing[6]. Formation of new granulation tissue following debridement may help to perpetuate the wound-healing cascade

Efficient debridement is an essential step in acute and chronic wound management. Chronic wounds are likely to require ongoing maintenance debridement rather than a single intervention[7]. The underlying pathogenic abnormalities in chronic wounds cause a continual build-up of necrotic tissue, and regular debridement is necessary to reduce the necrotic burden and achieve healthy granulation tissue. Debridement also reduces wound contamination and therefore assists in reducing tissue destruction[8]. Dead spaces that may otherwise harbor bacterial growth must be exposed during debridement. Various methods of debridement are available, each with its own advantages and limitations. The methods that are most efficient at removal of debris may, at the same time, be the most detrimental to fragile new growth, and in many cases, more than one method may be appropriate.

Hydrosurgery has been shown to be an efficient method of wound debridement and wound bed preparation[9]. The technology has been shown to be faster, more precise, and results in less tissue damage than other debridement methods[10]. Debritom+ (Medaxis AG, Baar Switzerland) is a hydrosurgery device that utilizes micro water jet technology that has been designed to debride acute and chronic wounds precisely and in a tissue-preserving manner. The system has a 510(k) approval by the FDA and a CE mark in Europe. With this technology, the water jet is fed with pressure through a tube connected to the main device to a non-return nozzle that generates a very fine water jet (Figure 1). The pressure that has been set is equal to the pressure prevailing before the point of entry into the nozzle. A recently published study found the micro water jet to help remove fibrin, necrotic tissue, and foreign bodies while leaving the granulating tissue unharmed allowing for faster wound healing in chronic, stalled wound[11]. The authors noted that debridement using micro water jet technology can be carried out with no or only minimal pain,

easily eliminated by simple local measures. Furthermore, the micro water jet application removes the need to touch the wound during debridement to minimize possible cross-contamination.

Figure 1. Micro water jet debridement device.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this prospective cohort study is to assess the clinical effectiveness of micro water jet technology in the debridement and healing of chronic wounds in terms of wound size, depth/extent, and percent wound reduction and healing. Additional assessments will include evaluating changes in leg rest pain score using a visual analogue scale (VAS); incidence of infection, and pain during debridement via the VAS scale as well as patient feedback regarding their debridement experience with micro water jet technology.

2.2 Exploratory Objective

The exploratory objective is to use near-infrared images of the wound (taken via $Snapshot_{NIR}$, a specialized near-infrared camera) for the characterization and measurement of tissue oxygenation that could enable correlation of wound tissue oxygenation before and after debridement with micro water jet technology (Section 3.2). Data from the exploratory objective may not be included in the clinical study report.

3. STUDY END POINTS

3.1 Primary Endpoints

The primary endpoints are to explore clinical efficacy and include:

1. The extent and size of ulcers (summation of the products of the long x short axis for all ulcers measured in centimeters squared, plus ulcer depth) will be evaluated and photographs of ulcers taken during screening and on all clinic visits up to 20 weeks or when the ulcer is healed, whichever is sooner.
2. Leg rest pain score – visual analogue scale (VAS) graded from 0 (pain free) to Grade 10 (maximum pain) during screening and on all clinic visits up to 20 weeks, or when the ulcer is healed, whichever is sooner.
3. Pain during Debridement score – VAS graded from 0 (pain free) to Grade 10 (maximum pain) during on all clinical visits when debridement is performed for up to 20 weeks, sooner pending wound healing.
4. Subjects feedback regarding their debridement experience with micro water jet technology will be collected on all clinical visits when debridement is performed.
5. Incidence of wound infection.

3.2 Exploratory Endpoint

Near-infrared images of the wound may be taken via the Snapshot$_{NIR}$ camera (Kent Imaging, Calgary, Alberta, Canada) before and after debridement pending camera availability. Snapshot$_{NIR}$ is a non-invasive imaging device that utilizes light in the near-infrared spectrum that harmlessly passes through the skin and is reflected off of the blood supplying the tissue to provide insight into the availability of oxygenated blood in the tissue (Figure 2). It is intended for use by healthcare professionals as a non-invasive tissue oxygenation measurement system that reports an approximate value of oxygen saturation, relative oxyhemoglobin level, and relative deoxyhemoglobin level in superficial tissue. Snapshot$_{NIR}$ is FDA and Health Canada cleared.

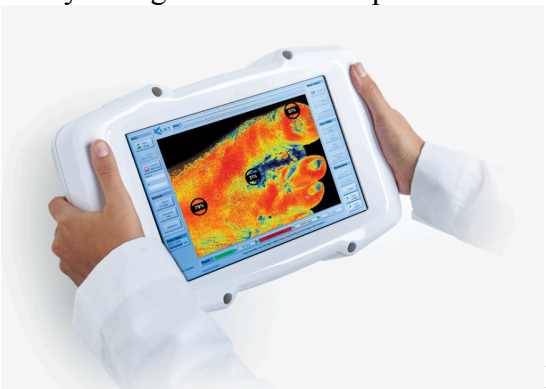


Figure 2. Snapshot$_{NIR}$ non-invasive imaging device

During the initial feasibility assessment using micro water jet technology for wound debridement, near-infrared images of the wound before and after debridement with the micro water jet technology were taken with the patient's consent (Figure 3a-d). Figure 3a is the pre-debridement clinical image of the wound after removing the dressing. Figure 3c is the pre-debridement near-infrared image of the wound after removing the dressing. The oxygenation of the tissue in the central aspect of the wound was measured to be 79%, and the image depicted a small area of oxygenated tissue (darker shade) around the wound. Figure 3b is a post-debridement clinical image of the wound. Figure 3d is the post-debridement near-infrared image

of the wound using micro water jet technology. The oxygenation of the tissue in the central aspect of the wound was measured to be 96% and the area of oxygenated tissue (darker shade) around the wound had almost doubled in size.

Figure 3a. Pre-debridement

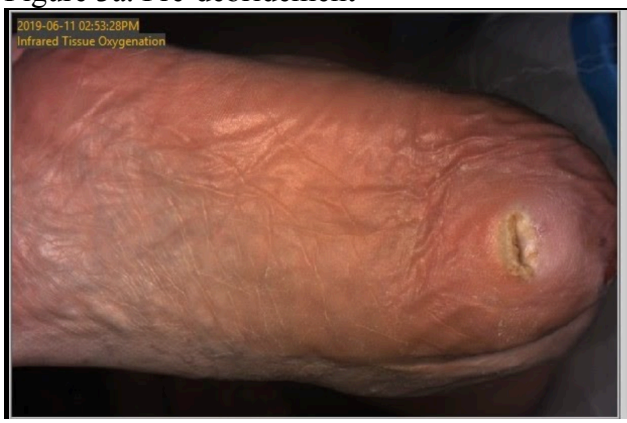


Figure 3b. post-debridement

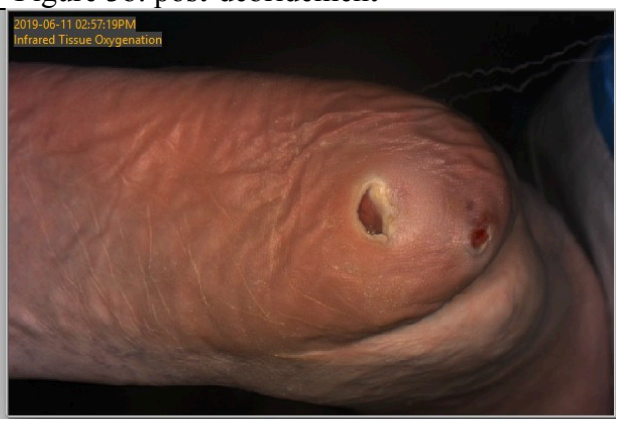


Figure 3c. Pre-debridement tissue oxygenation

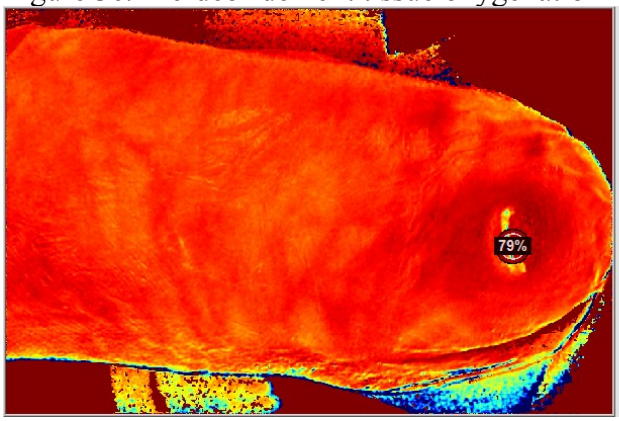
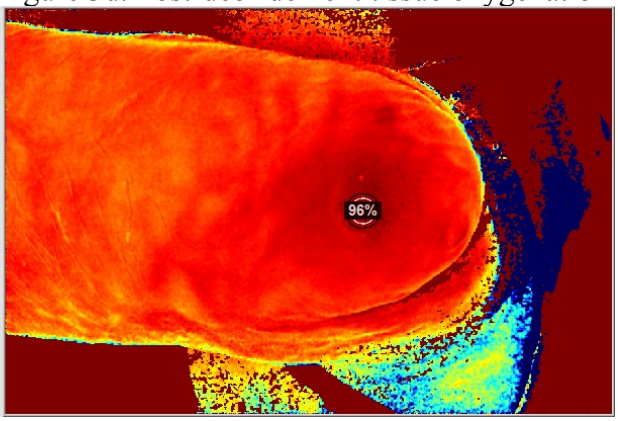


Figure 3d. Post-debridement tissue oxygenation



The near-infrared wound images are for exploration into the characterization and measurement of tissue oxygenation that could enable correlation of wound tissue oxygenation before and after debridement with micro water jet technology. Analysis of the near-infrared wound images will include examination of the percentage and extent of tissue oxygenation before and after debridement in response to micro water jet technology debridement.

4. OVERALL STUDY DESIGN

4.1 Study Design

This is a prospective cohort, single-center, open-label study in subjects with chronic lower extremity wounds. The study will enroll up to 20 subjects. Subjects will undergo screening evaluations to determine eligibility to enroll in the study. All study subjects will receive micro water jet technology debridement as opposed to other debridement methods as part of their wound care treatment. The other aspects of subjects wound care protocol will remain unchanged. In the case of bilateral limb ulcers, or multiple ulcers, subjects will have the option to receive micro water jet debridement on one or all of the ulcers.

Clinical efficacy analyses will include assessment of changes in the extent and size of ulcers, percentage healing and rate of healing, leg rest pain score using VAS scale, pain experience during debridement using VAS scale, incidence of wound infection (See Section 3).

Safety assessments, including AE reporting, physical examination, vital sign measurements, concomitant medications will be performed at all clinical visits throughout the study.

4.2 Study Duration

Up to 20 weeks, sooner pending wound healing as defined by 100% re-epithelialization.

5. STUDY PROCEDURE

5.1 Recruitment

Patients will be recruited by the study investigators and by research coordinators at the Rosalind Franklin Health Clinic. Patients will be invited to participate and the investigator or research staff will discuss the study design, duration and risks of participating in the study. The subject will then be provided with a consent form to read at their leisure. The investigator or research coordinator will be available to answer questions and provide more explanation as requested by the potential study subject and their family.

5.2 Informed Consent

Informed consent will be obtained by the study coordinator prior to any screening measures. Discussion of the study will be done in a private room. The subject will be allowed to read the consent at their leisure and discuss it with family members before they make a decision. If the patient agrees to participate, we will provide them with a copy of the consent, a copy will be placed in the medical record and a copy will be placed in the patient's study folder.

5.3 Study Participants

20 patients with chronic lower extremity ulcers will be recruited for this prospective cohort at the Rosalind Franklin Health Clinic to receive micro water jet technology debridement as part of their wound care treatment plan after being informed of the study and providing informed consent.

Inclusion Criteria and Population:

a) Male or female age 18 or older

b) The ability and willingness to provide Informed consent

c) Presence of a chronic lower extremity ulcer

Chronic ulcer is defined as that ≥ 4 weeks in duration.

Subject's informed consent for participation prior to proceeding with micro water jet technology debridement

d) Patient's ulcer cannot exhibit any gross clinical signs of infection.

e) Patient is willing to participate in all procedures and follow up evaluations necessary to complete the study.

f) Patient willing and able to comply with having micro water jet technology debridement potentially weekly or biweekly as part of their wound care treatment plan for up to 20 weeks.

Exclusion Criteria:

a) Patients with active wound infection, or untreated osteomyelitis

b) Patients with dementia, or impaired cognitive function

c) Patients who are unable or unwilling to participate in all procedures and follow up evaluations

d) Patient has Active Charcot foot

e) Patient with malignant wounds

5.4 Subject events after entry:

Screening/ Pre-debridement:

Subjects will be screened to ensure that they meet the inclusion and exclusion criteria. The study will be explained and written informed consent obtained from each patient prior to the initiation of screening procedures.

Following the screening, subjects will receive baseline evaluation/assessment as part of the general clinic visit and treatment initiation. Baseline evaluation/ assessment will include recording of clinical observations.

Clinical Observations and Recording:

1. Wound size and appearance:

   Wound dimensions, locations, and characteristics will be documented prior to commencement of the study and assessed weekly or biweekly. Ulcer assessments include wound measurement, photographs, proportion of granulation tissue, and dressing changes.

2. Physical exam:

   Physical exam will be conducted, including vascular, dermatological, deformities and range of motion, neurological, and infection assessments, as part of a regular wound care visit.

***Medical History**:* A detailed medical history will include: previous history, location and duration of previous ulcers, amputation (toe, foot, below knee, above knee), lower extremity bypass, lower extremity angioplasty, CABG, cardiac angioplasty, last visit by physician (in weeks), and current/past use of special shoes or insoles.

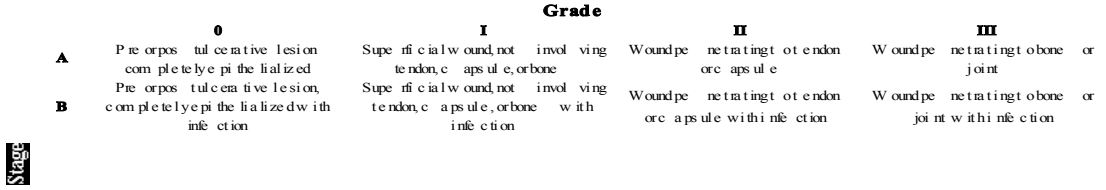
***Neurological Evaluation**:* The Neurological assessment will consist of Vibratory Perception Threshold testing (VPT) using the technique described by Young[12], and the 10 gram Semmes-Weinstein monofilament using the criteria described by Armstrong and Lavery[13]. The presence of sensory neuropathy will be identified as vibratory perception threshold greater than 25 volts or inability to accurately perceive a 10 gram Semmes-Weinstein monofilament at 1 or more of 10 test sites on the sole and dorsum of the foot.

Vascular Assessment: The vascular assessment will consist of palpation of the dorsalis pedis and posterior tibial arteries and non-invasive Doppler studies. Ankle Brachial Index (ABI) will be performed of both extremities.

***Deformities & Joint Range of Motion**:* Range of motion of the ankle, subtalar and first metatarsophalangeal joint will be assessed using standard landmarks and procedures. We will define hallux rigidus as first metatarsophalangeal joint dorsiflexion less than 65 degrees. Toe and metatarsophalangeal joint deformities will be defined as present when a rigid, non-reducible deformity exists.

***Wound Classification**:* The site investigators will evaluate the wounds. Wounds will be classified according to the University of Texas Wound Classification System (Table 1). Although this classification system was originally described for diabetic foot ulcers, this the only validated wound classification system and will be adapted for the purpose of this study.[14]

Table 1: The University of Texas Diabetic Wound Classification System[14, 15]



3. Monitoring diabetic control (where appropriate):

No specific attempts to improve glucose control will be made during the study by the investigators. Glucose control will not be used as an exclusion criterion. We feel that this more accurately reflects the diabetic foot ulcer population. Consultations to primary care physicians and sub specialist will be provided as needed. Patients will be encouraged to control their diabetes as well as they can and to contact their usual care provider for symptomatic hyperglycemia, hypoglycemia or other diabetes-related problems. Any changes in diabetes management will be recorded. Patients will monitor their diabetes control in their usual manner.

4. VAS pain scale:

Patient's pain associated with the ulcer will be assessment and documented via the VAS pain scale. Patient's pain and subjective comments associated with micro water jet technology debridement will also be assessed and documented.

5.5 Treatment

Following base assessment, the wound will be debrided using micro water jet technology. An initial test of sterile saline will be sprayed onto the patient's hand so the patient can get a feel for the force of the water jet and know what to expect. Topical analgesic (lidocaine) will be administered to the wound area prior to debridement as needed. Micro water jet technology will be used to remove all devitalized, necrotic tissue and until extremely fine bleeding develops. A protective shield will be used to prevent spread of the aerosol formed after the stream of sterile saline comes into contact with the wound (Figure 4). Both the hand piece delivering the sterile saline stream and the protective shield are one-time use disposable items. Treatment times will be dependent on the wound size and level of contamination. A previously published retrospective study noted the treatment duration to be between 1 and 22 minutes utilizing 100-200mL of sterile saline as rinsing fluid[11]. Hemostasis will be controlled via pressure. Appropriate wound dressings will then be applied. Caution will be used in patients with uncontrolled hypertension and patients on anticoagulation therapy or acetylsalicylic acid medication. While debridement is not contraindicated in these patients, there may be a higher risk of excessive bleeding. Compression will initially be used to control hemostasis followed by an alginate or a hemostyptic agent.

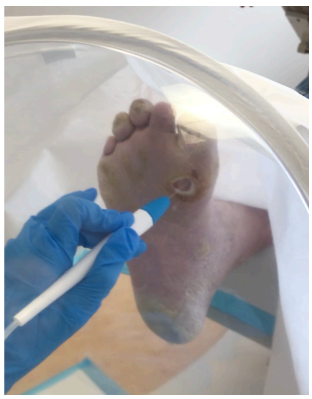


Figure 4.
Debridement of wound using micro water jet technology. A protective shield is used to prevent the spread of the aerosol formed after the stream of sterile saline comes into contact with the wound.

5.6 Subsequent visits

Patients will return to clinic every one to two weeks (+/- 2 days) as part of their regular wound care treatment plan for follow up assessment including wound evaluation and photograph. Wounds will be subsequently debrided using micro water jet technology if deemed appropriate by the investigators followed by a dry sterile dressing as previously described. Wound will be followed for a total of 20 weeks or when the wound has completely healed, as defined by 100% re-epithelialization.

5.7 End of study visit

At the end of the 20-week evaluation, patients with open wounds will return to clinic on Day 112 (+/- 2 days) for the end of study visit. In cases of complete wound healing or patient withdraw, the end of study evaluation will take place at the patient's last day of study visit and will occur prior to Day 112. The following assessments will occur at the End of study visit:

1. Wound evaluation and photograph
2. VAS pain scale
3. Wound debridement (if applicable)

A wound dressing, if deemed necessary by the investigator will be applied.

5.8 Adjunctive Care:

All patients will receive standard adjunctive therapy for lower extremity ulcerations. Efforts will be made to control any edema by limb elevation, diuretic medication or compression hose, as indicated. Patients will be advised to stay off the affected foot as much as possible, and asked to avoid walking, except as absolutely necessary. Patients will be offered other assistive modalities at the time of enrollment (crutches, canes, and walkers) to enhance postural stability.

5.9 Cost/Compensation to Participants

There are no anticipated costs to the patient. Wound debridement procedure is reimbursed by CMS under CPT code 11042. The micro water jet device and disposable accessories are provided by Medaxis AG as part of the study. We do not anticipate any possible injury to the patient or other liability that could accrue to the patient under the normal process of care. Participant will be paid $50 total for participating in the study.

6.0 SAFETY

6.1 General Protection

Wound care instructions will be reviewed at every visit to ensure patient compliance with the study protocol. Patients will be instructed to inspect the wound at each dressing change and on how to detect signs of wound deterioration, and to immediately report these signs to the investigator. If the ulcer worsens, medical treatment as needed, will be initiated by the investigators. At each visit the patient will be questioned about potential adverse experiences with the response recorded in patient's chart. This includes exacerbation of existing condition or event. Infection of soft tissue or bone, amputation, need for incision and drainage, iatrogenic ulcer formation, or deterioration of the wound will be considered as an adverse event. The patient will also be questioned as to any problems, adverse experiences, or digressions from the study procedures and restrictions. Relevant findings will be noted in the patient's chart.

6.2 Interim Visits

If a subject experiences significant wound deterioration between scheduled study visits, the patient will be instructed to telephone the investigator immediately to arrange for an interim visit. Further treatment of the ulcer will be prescribed at the discretion of the investigator. Patients may be removed from the study if the situation warrants.

24 hour "paging system" Subjects will be instructed to call the Rosalind Franklin University Health Clinics if they have any questions or concerns. The Rosalind Franklin University Health Clinic has an after-hour answering service for patient emergencies where the on-call physician for the research group will be alerted of the situation. If a subject experiences any wound related irritation or complications, they will be urged to contact the clinics for an interim visit. Patients may be removed from the study if the situation warrants.

6.3 Potential Risks

Potential risks include wound or systemic infection and deterioration of wound. Any wound deterioration, or infection will be addressed with appropriate local and systemic therapy, as warranted. Evidence to support the diagnosis of wound deterioration, infection, abscess, or osteomyelitis would be considered an adverse event and recorded accordingly. Any cultured organism and antibiotic therapy will be recorded. Infection will be treated with aggressive debridement and appropriate systemic antibiotics as required until the infection has resolved. Microbiology confirmation will be recorded. Choice of antibiotic therapy is at the investigator's discretion. A wound culture will also be obtained (via curettage at the ulcer base, after wound debridement) if any signs of wound infection exist.

6.4 Removal of Patients from Therapy or Assessment

All patients are free to withdraw from participation in this study at any time, for any reason and without prejudice. The Investigator may terminate a patient from the study for administrative reasons, or in the Investigator's opinion, to protect the patient's best interest. If a patient is withdrawn before completing the study, the reason for withdrawal will be entered into patient's chart and reported accordingly. Whenever possible and reasonable, the evaluations which were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

7.0 DATA HANDLING AND RECORDKEEPING

7.1 Data and Safety Monitoring Plan

We plan to use the NIDDK 'Data & Safety Monitoring (DSM) Guidelines for Clinical Trials'. Dr. Wu will evaluate the data on an ongoing basis and quarterly reports will be prepared to evaluate the progress of the trial (accuracy of data, verifying consent of subjects, and adherence to protocol schedule.). Clinical and patient data will be maintained, segregated and secured in locked filing cabinets only accessible to the Investigators. Patient records will be held as strictly confidential and names, or other identification, will not be used for publication or other purposes. All employees related to this grant request will be certified in accord with the NIH Human Participants Protection Education for Research Teams.

7.2 Patient Confidentiality

Upon entering the study each patient will be assigned a sequential number under which all study data will be stored. No personal identification information will be used. All information collected for this study will be secured in a locked office. Only the investigators and other members of study, independent ethics committees and inspectors from government regulatory agencies will be able to access patient medical records.

7.3 Ethics

This study will be conducted in compliance with the Declaration of Helsinki and its amendments, the International Conference on Harmonisation (ICH) principles of Good Clinical Practice (GCP) (including archiving of essential study documents) and the applicable regulations of the country in which the study is conducted.

A properly constituted, valid Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must review and approve the protocol, the Investigator's informed consent form (ICF) and related patient information and recruitment materials before the start of the study.

It is the responsibility of the Investigator to ensure that written informed consent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

8.0 STATISTICAL ANALYSIS

8.1 Sample Size Estimation:

Previous work done suggests that a small case series of 16 patients is adequate as a pilot trial. Accounting for a 20% potential fall out rate means that a total of 20 subjects should be enrolled into the study.

8.2 Data Analysis

Data analysis will include descriptive statistics and Chi-square and Fisher's exact tests for categorical variables. Continuous variable will be assessed using the Student t test, and where possible linear regression models. Outcomes variables will be compared with repeated measures of analysis of variance tests. Statistical significance will be accepted for p values $<.05$.

9.0 REFERENCES

1. Wound Healing Society. 2006. Guidelines for the best care of chronic wounds. *Wound Rep Reg* **14**: 647-710.

2. Mustoe, T.A., K. O'Shaughnessy and O. Kloeters. 2006. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. *J Plast Reconstr Surg* **117**: 35-41.

3. Brem, H. and M. Tomic-Canic. 2007. Cellular and molecular basis of wound healing in diabetics. *J. Clin. Invest.* **117**: 1219-22.

4. Hunt, T.K., H. Hopf and Z. Hussain. 2000. Physiology of wound healing. *Advances in Skin and Wound Care* **13**: 6-11.

5. O'Brien M: Methods of debridement and patient focused care. J Comm Nurs 17(11): 17-25, 2003.

6. G.S.Schutz, et al., Wound bed preparation: a systemic approach to wound management, Wound Rep Reg Supplemental, 2003;11:1-28

7. Falanga V, Brem H, Ennis WJ, Wolcott R, Gould LJ, Ayello EA. Maintenance debridement in the treatment of difficult-to-heal chronic wounds. Recommendations of an expert panel. Ostomy Wound Manage. 2008 Jun;Suppl:2-13; quiz 14-5.

8. Werdin, F., M. Tennenhaus, H. Shaller and H. Rennekampff. 2009. Evidence-based management strategies for treatment of chronic wounds. *Journal of Plastic Surgery* **9**: 209-179.

9. N.S. Sivrioglu Jrkören, Versajet hydrosurgery system in the debridement of skin necrosis after Ca gluconate extravasation: report of 9 infantile cases, Acta Orthop. Traumatol. Turc. 48 (l) (2018) 6–9.

10. Granick MS, Jacoby M, Noruthrun S, Datiashvilli RO, Ganchi PA. Clinical and economic impact of hydrosurgical debridement on chronic wounds, Wounds 18 (2) (2006) 35–39.

11. Reber M, Nussbaumer P. Effective debridement with micro water jet technology (NWT): A retrospective clinical application observation of 90 patients with acute and chronic wounds. Wound Medicine, 20(2018);35-42.

12. Young MJ, Breddy JL, Veves A, Boulton AJ. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. *Diabetes Care.* 1994;17(6):557-560.

13. Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, Fleischli JG. Choosing a Practical Screening Instrument to Identify Patients at Risk for Diabetic Foot Ulceration. *Archives of Internal Medicine.* 1998;158:289-292.

14. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation [see comments]. *Diabetes Care.* 1998;21(5):855-859.

15. Lavery LA, Armstrong DG, Harkless LB. Classification of Diabetic Foot Wounds. *J Foot Ankle Surg.* 1996;35(6):528-531.