A PROSPECTIVE, OPEN LABEL, MULTICENTER TRIAL FOR EVALUATING THE EFFICACY OF TREATING AND MANAGING WOUNDS IN ELDERLY POPULATION IN SPECIALIZED NURSING FACILITIES USING REDDRESS WOUND CARE SYSTEM (RD1)

NCT04577183

AUGUST 13, 2018

Authorization				
	Name	**Title**	**Signature**	**Date**
Written By:	Sharon Sirota	CTL		
Approved By:	Alon Kushnir	CEO		

Revision History			
Rev. No.	**p.No & section**	**Description**	**Date**
1		NEW	19 Jun 2018 (Approved by FDA on 27 Jun 2018
2	14, 2.1.16	Removed: Dialysis removed from exclusion criteria	13 Aug 2018
	8, 1.3-Subject population	Added: Patient that require Legally Authorized Representative (LAR)	
	Appendix 2: RD1 Application Protocol, RD1 Preparation	Added: Two FDA cleared 8.5ml vacuum tubes with ACDA Solution. Added throughout the appendix	
	Appendix 2: RD1 Application Protocol, P.27 Table 1	Changed: RD1 diameter units changed from cm^2 to cm	

RedDress Wound Care System
Protocol RD004

Dated 19 June 2018

A Prospective, Open Label, Multicenter trial for evaluating the Efficacy of Treating and Managing Wounds in Elderly Population in Specialized Nursing Facilities Using RedDress Wound Care System (RD1)

Principal Investigator: Dr.Bryan Doner, DO
Tel: 412-496-6365
Fax: 724-543-8802
Email: drdoner@dandpmedicalgroup.com

Sponsor: RedDress LTD.
Contact Person: Alon Kushnir
Tel: (972) 547800252
alon@reddress.co.il

CONFIDENTIAL

PROTOCOL APPROVAL FORM

Study Number: RD-004

Study Name: A Prospective, Open Label, Multicenter trial for evaluating the Efficacy of Treating and Managing Wounds in Elderly Population in Specialized Nursing Facilities Using RedDress Wound Care System (RD1)

This Protocol has been reviewed and approved by the following:

_____ _____

Dr. Bryan Doner, DO Date
Principal Investigator

Contents

INTRODUCTION

In order for a wound to heal multiple processes must work in concert. The tissue must receive adequate arterial flow, the bacterial burden must be controlled, the environment must have a proper moisture balance, and negative mechanical forces must be eliminated. Wounds can vary in size and depth; wounds can be clean with a predominance of healthy granulation tissue or have nonviable or necrotic material present, which inhibits healing.

The acute wound which is common, heals in a predictable and orderly fashion. Healing begins with initiation of the clotting cascade, which in turn results in the proteolytic cleavage of fibrinogen by the enzyme thrombin, forming an insoluble blood clot. The blood clot holds damaged tissues together and provides the provisional matrix required for the natural healing process. In addition the outer layer of the clot dries out and creates a degradable crust formed from erythrocytes and other blood components. This tough shell protects the wound from contact with environmental hazards, reduces pain, protects the wound from bacterial contamination, and enables a moist wound environment under it, allowing the repair process to take place unhindered. The clot is a provisional extracellular matrix (ECM), which harbors cytokines and growth factors released by the degranulation of activated platelets and other cells within the clot. The acute wound beneath the clot heals and the remaining dry crust is shed exposing the reconstructed skin.

Chronic wounds such as diabetic ulcers, pressure ulcers and venous ulcers, on the other hand do not heal or heal slowly because an underlying defect (e.g. diabetes mellitus, continued pressure that impedes local blood flow and vascular problems.) arrests progress through the phases of wound healing. Most commonly chronic wounds stall in the inflammatory phase of wound healing characterized by the presence of non-viable tissue, excessive bacterial burden, and the presence of increased inflammatory cytokines.

With aging comes a 20% loss in dermal thickness, making the skin of many elderly adults almost transparent in appearance. The subcutaneous fatty layer also becomes thinner, especially on the face, neck, back of the hands, and shins. If traumatized, these areas will absorb more energy than other parts of the body because they lack cushioning fatty subcutaneous tissue; thus, they are at increased risk for an injury such as a skin tear. The skin has less resilience – sufficient force exerted against the skin will result in a tearing-type injury. Once a skin tear is present in the elderly, the slower rate of epidermal cell turnover prolongs healing time. Alterations in collagen and protein synthesis also may contribute to delayed skin tear healing. In addition, the skin's microcirculation collapses, increasing risk of bruising and reducing blood supply to the skin (the latter can prolong healing time if a break in the skin occurs). Because of the decreased immune response of the geriatric patient, skin tears have a higher risk of becoming infected than in the non-geriatric patient

The formation of a whole blood clot occurs through a cascade of events. Two pathways lead to the formation of the final blood clot: the intrinsic and extrinsic pathways. Although they are initiated by different distinct mechanisms, the two converge on a common pathway leading to the same fibrin clot formation. The clot formation on an acute wound is through the extrinsic pathway while the in vitro clot formation is through the intrinsic pathway.

A blood clot is the body's natural and optimal provisional wound matrix. As described above, it protects the wound and serves as a provisional matrix into which cells can migrate. The use of the RD1 as a provisional matrix in the management of chronic wounds recreates the natural healing process. Moreover, the function of a blood clot as a provisional matrix has been validated and reported extensively in literature and in 2 clinical studies conducted with the RD1. There are several commercial available matrix or scaffold products. However, all of these products are derived from foreign material: animal tissue or human donor skin. An autologous blood clot matrix should have no immunologic rejection or risks associated with the use of animal products.

The RD1 is created by drawing the patient's blood with the use of citrate anticoagulant. The anticoagulant allows the clot to form later in a controlled fashion—citrate is a widely used anticoagulant. The blood is then placed in the clotting tray (within few minutes) and the coagulation is facilitated by adding calcium and kaolin (insoluble aluminum silicate). The forming clot assumes the shape of the tray containing it, and can then be applied to the wound, and then covered with primary and secondary dressings.

The use of the citrate anticoagulant is essential to the process. Withdrawing blood without the use of an anticoagulant would immediately initiate the coagulation cascade and within minutes a whole blood clot would form. Citrate, which is widely used in the blood banking industry, prevents clotting by binding calcium ions. Clotting can be re-initiated in vitro by adding the calcium ions to the citrated blood. The clotting time can be further accelerated by mixing the blood with a contact surface such as kaolin (insoluble aluminum silicate).

The investigational product, the RD1 kit, was designed to enable a care provider to create an in vitro blood clot from the patient's own blood at the point of care, in a safe and effective manner. The RD1 kit involves currently accepted medical procedures of halting the coagulation process and re-initiating the natural occurring process.

The proposed protocol (RD004) should be sufficient to determine the safety of RD1 in wounds of various etiology, such as Diabetic foot ulcers, pressure ulcer, venous ulcers and skin tears. This takes into account the suppositions that the proposed product is natural in origin (i.e., not synthetic), is not derived from animals but is autologous, and that it attempts to mimic the body's own healing mechanisms of replacing missing Extra Cellular Matrix (ECM) with a fibrin-based matrix, a defect which exists in the local areas of chronic ulcers. Furthermore the RD1 safety was validated in 2 clinical studies of 30 patients with wounds of various etiologies.

1. OVERVIEW

1.1. Study Objectives

Primary Objective
The primary objective of this protocol is:

1. Efficacy- The performance of RD1 in terms of wound progress towards closure in wounds deemed suitable for treatment with RD1

Secondary Objectives:
Secondary objectives of the trial are:

1. Safety - Determine complication rates for all adverse events compromising serious adverse events, adverse events (AEs), and device-related adverse events (DRAEs); AEs include any lack of venous access events
2. Efficacy - Assess the incidence of complete wound closure at 16 weeks for wounds treated with RD1 (defined as skin re-epithelialization without drainage or dressing requirements).
3. Efficacy - Assess the wound Percent Area Reduction (PAR)
4. Efficacy- Assess the optimal duration between applications of RD1 per wound parameter
5. Efficacy- Assess the need of design and procedure improvements of the RD1 for specialized nursing facilities (SNF)
6. Sub Group Analysis – asses the safety and efficacy per wound etiology
7. Asses the cost of RD1 procedure in SNF compared to cost of treatment before RD1
8. Assess wound pain compared to wound pain during treatment before RD1
9. Assess medical staff wound related weekly labor of wound treatment before and during RD1.

1.2. Study Design

The study is a prospective, single arm, multicenter efficacy study, consisting of 60 subjects who will complete the study (note: if any patients are lost to follow-up or withdrawn, enrollment will increase to compensate for loss of these subjects). The subjects will receive up to 16 RD1 applications. In case of complete healing, subject will be called for one confirmatory visit two weeks later or before discharge from the SNF (the earlier of the two). Subject data will be kept in each site's records.
All diabetic subjects' glycemic management will be performed by a qualified physician. All subjects will have wound care specialist or wound surgeon or dermatologist involved in their wound care

1.3. Subject Population

Up to 120 (or more) subjects will be enrolled at 2 SNF in the US in 2 phases: Phase I- 40 subjects and phase II- 80 subjects). Subjects will be older than 18 years with wounds deemed suitable for treatment with RD1.

1.3.1. Patient that require Legally Authorized Representative (LAR)

The patient population that will be enrolled to the study includes patients that require LAR signature. The rational for inclusion of this population is that the RD1 is an FDA cleared product, that demonstrated significant chronic ulcers healing rates, much superior to known standard of care. In the nursing home, many of patients with chronic ulcers are those that require LAR. By not including those patients in the RD1 study, we are depriving them from

superior treatment and with the prospect of healing their ulcers and we are discriminating them from those patients that do not require LAR. The RD1 was determined by FDA to be a safe product and will be used in the study according to the FDA cleared intended use only.

Enrollment process of patients that require LAR will be according to the local regulations and enrollment procedure per site will be submitted to the IRB in advance including specific requirements in the ICF and the consenting process.

1.4. Study Duration

The study is expected to last 12 to 24 months.

The study per each subject will continue for up to 16 weeks of RD1 treatment (not including up to 2-week screening period (± 2 days)), Any wounds that are considered initially healed within the 16-week period will require a confirmatory visit two weeks after healing of before discharge from the SNF (the earlier of the two) to assess durability of wound closure.

Patients will be treated with RD1 every 7 days (±3 days), investigator can prolong the duration between treatments based on medical decision. Total treatment duration is up to 16 weeks or until complete healing.

1.5. Treatment Regimen

Ethics/Institutional Review Board (IRB/EC) committee approved consent is obtained prior to subject participation. The patients will be screened to determine if they meet the inclusion and exclusion criteria. The screening period lasts for up to 14 days ± 2 days. The target ulcer will be treated with RD1. The RD1 clot is created from the subject's blood in accordance with the procedure described in the RD1 Application Protocol (Appendix 2) and according to accepted precautions guidelines. Patients will be treated with RD1 every 7 days (±3 days), investigator can prolong the duration between treatments based on medical decision. Total treatment duration is up to 16 weeks or until complete healing. The RD1 should be anchored using steri-strips then covered with a primary non-adherent dressing such as Mepitel and then covered using a secondary dressing based on type of wound and amount of exudate.

1.6. Assessment

1.6.1 Screening Phase:

1.6.1.1 Written informed consent.

Informed consent will be obtained by the principal investigator or his or her designee prior to any study-related procedures. When the subject or his/ her legal authorized representative is agreeable to participation in the clinical trial, he/she must understand, sign and date the IRB/EC–approved Informed Consent Document (see sample in Appendix 1), which describes the study and potential

discomforts, risks, and benefits of participating. One copy of the consent form will be provided to the subject and one copy will be maintained with the subject's medical record.

1.6.1.2 Execution of inclusion and exclusion criteria.

1.6.1.3 Complete medical history and physical examination.

1.6.1.4 Collection of patient demographics.

1.6.1.5 Complete ulcer history.

1.6.1.6 Wound photography before cleansing/ debridement. See Appendices 3-4.

1.6.1.7 Wound cleansing

1.6.1.8 Wound debridement, if required (Debridement procedures are described in Appendix 9).

1.6.1.9 Wound measurement via digital photography. See Appendices 3-5.

1.6.1.10 Wound depth measurement by accepted method. Unit of measurement is millimeters

1.6.1.11 Wound photography after cleansing/ debridement. See Appendices 3-4.

1.6.1.12 Classification and grading of study wound (if applicable).

1.6.1.13 Neuropathic assessment (for foot ulcers only).

1.6.1.14 Review of ulcer and blood related medications taken by the subject including herbal medications.

1.6.1.15 Pregnancy test (urine) for female subjects of child-bearing potential.

1.6.1.16 Assessment for infection of the target ulceration.

1.6.1.17 Assessment of moisture control, when relevant.

1.6.1.18 Assessment of offloading, when relevant.

1.6.1.19 Vascular perfusion assessments will be conducted to assess adequate perfusion of the lower extremities using Ankle-Brachial Index (ABI), when relevant. ABI will be determined on the affected side (i.e., the side of the body on which the study ulcer resides) according to standard procedure/protocol at the study site.

1.6.1.20 Laboratory. Patients who have had labs drawn within 30 days prior to screening do not require a repeat draw. Otherwise complete blood count, PT, PTT, and HbA1c will be obtained.

1.6.1.21 X-Ray of the study ulcer will be performed in cases of suspected osteomyelitis.

If the X-Ray is inconclusive regarding osteomyelitis, further investigation can be undertaken at the discretion of principal investigator. As stated below in the exclusion criteria, patients with underlying osteomyelitis will be excluded.

1.6.1.22 During the screening period the wounds will be treated weekly with standard of care treatment .

1.6.1.23 Investigator subjective wound pain assessment (appendix XX)

1.6.1.24 Medical staff wound related weekly labor assessment for the week prior to initiation of the screening (appendix XX) (optional per sponsor instruction)

1.6.1.25 Wound treatment cost assessment for the period prior to initiation of screening (at least weekly cost, preferably monthly cost, if

possible- cost since start of wound treatment)-)optional per sponsor instruction).

1.6.2 Treatment Phase Initial (Day 0):

1.6.1.1 Adverse event assessment.
1.6.1.2 Ulcer and blood related concomitant medication review.
1.6.1.3 Investigator subjective wound pain assessment
1.6.2.1 Photography before and after cleansing and debridement (if applicable)
1.6.2.2 Wound measurement by photography. Two measurements- before and after cleansing and debridement.
1.6.2.3 Wound depth measurement by accepted method. Unit of measurement is millimeters. Two measurements- before and after cleansing and debridement
1.6.2.4 Ulcer cleansing
1.6.2.5 Ulcer debridement as needed
1.6.2.6 Application Regimen: as per the investigators Brochure. Up to 3 RD1 dressings can be applied on each wound on each visit, according to wound size and investigator decision of subject health. The RD1 will be removed or applied only by the research staff.
1.6.2.7 Wound related staff labor assessment (optional per sponsor instruction)

1.6.3 Treatment Phase. (Weeks 1-16): The following treatments and assessments are performed during the treatment phase weeks 1-16. During the treatment phase there are 2 types of visits: **1.** RD1 Change Assessment Visit **2.** RD1 Change Visit (performed immediately after Change Assessment Visit).

1.6.3.1 RD1 change assessment visit procedures every 7 days (±3 days):

1.6.3.1.1 RD1 change will be assessed by investigator
1.6.3.1.2 Wound/ blood related adverse event assessment
1.6.3.1.3 Assess offloading compliance when applicable.
1.6.3.1.4 Assess moisture control when applicable.
1.6.3.1.5 Ulcer and blood related concomitant medication review.
1.6.3.1.6 Photo the RD1 on the ulcer.
1.6.3.1.7 Assessment of the edges of the wound to assess infection.
1.6.3.1.8 Assessment of the adherence of the RD1 to the wound.

1.6.3.2 RD1 re-application visit procedures (occurs if investigator decides to change RD1, should occur immediately after RD1 change assessment visit):

1.6.3.2.1 Investigator subjective wound pain assessment pre RD1 removal
1.6.3.2.2 Removal of old RD1
1.6.3.2.3 Photography after RD1 removal, before cleansing and debridement.
1.6.3.2.4 Wound measurement by photography. Two measurements- before and after cleansing and debridement.
1.6.3.2.5 Wound depth measurement by accepted method. Unit of measurement is millimeters. Two measurements- before and after cleansing and debridement
1.6.3.2.6 Wound assessment.
1.6.3.2.7 Ulcer cleansing.
1.6.3.2.8 Ulcer debridement as needed.
1.6.3.2.9 Assess wound infection.
1.6.3.2.10 Application Regimen: as per the investigators Brochure. Up to 3 RD1 dressings can be applied on each wound on each visit, according to wound size and investigator decision of subject health. The RD1 will be removed or applied only by the research staff.
1.6.3.2.11 Assessment of wound closure
1.6.3.2.12 Wound related staff labor (optional per sponsor instruction)
1.6.3.2.13 RD1 clot residues sent to analysis

1.6.3.3 **Wound healing confirmatory visit.** Will be performed to assess durability of wound closure. Performed at the earlier of the 2 options: 1. before discharge from SNF. 2. Two weeks after complete healing. For wounds that have healed during the 16 weeks of active treatment.

1.6.3.3.1 Wound size measurement by photography.
1.6.3.3.2 Wound depth measurement by accepted method. Unit of measurement is millimeters
1.6.3.3.3 Investigator assessment of healing
1.6.3.3.4 Physical examination
1.6.3.3.5 Adverse event assessment.
1.6.3.3.6 Assess offloading compliance.
1.6.3.3.7 Concomitant medication review.
1.6.3.3.8 Laboratory: complete blood count, PT, PTT, and HbA1c
1.6.3.3.9 Offloading (for up to 2 weeks after wound healing, when applicable
1.6.3.3.10 Investigator subjective wound pain assessment
1.6.3.3.11 Wound related staff labor during the whole RD1 treatment period (optional per sponsor instruction)
1.6.3.3.12 Wound treatment cost during the whole RD1 treatment period

1.6.3.4 End Of Study/ Early Termination Visit: At the end of week 16, for wounds that have not healed during the 16 weeks of active treatment or for early termination from the study, perform:

1.6.3.4.1 Investigator subjective wound pain assessment pre RD1 removal
1.6.3.4.2 Removal of old RD1
1.6.3.4.3 Wound size measurement by photography. Two measurements- before and after cleansing and debridement
1.6.3.4.4 Wound depth measurement by accepted method. Unit of measurement is millimeters. Two measurements- before and after cleansing and debridement.
1.6.3.4.5 Investigator assessment of healing
1.6.3.4.6 Physical examination.
1.6.3.4.7 Adverse event assessment.
1.6.3.4.8 Assess offloading compliance.
1.6.3.4.9 Ulcer and blood related concomitant medication review.
1.6.3.4.10 Laboratory: complete blood count, PT, PTT, and HbA1c
1.6.3.4.11 Wound related staff labor during the whole RD1 treatment period (optional per sponsor instruction)
1.6.3.4.12 Wound treatment cost during the whole RD1 treatment period (optional per sponsor instruction)

2. SELECTION CRITERIA

All of the study's inclusion and exclusion criteria must be met by Day 0 (first visit) for the subject to be eligible for the treatment phase of the study.

2.1. Inclusion Criteria

2.1.1 Subject is ≥18 years of age
2.1.2 Patient with a wound deemed suitable for treatment with RD1
2.1.3 Prior to inclusion of an ulcer in the study, each wound will be reviewed for eligibility by an independent assessor using a central online review process that includes images of the ulcer.
2.1.4 Ulcer free of clinical signs of infection. (Subjects with wound infection at the screening visit may be treated and re-screened for participation in the study after eradication of the infection).
2.1.5 Post-debridement, ulcer free of necrotic tissue.
2.1.6 For foot ulcers, Subject has adequate vascular perfusion of the affected limb, as defined by Ankle-Brachial Index (ABI) ≥ 0.65 and ≤ 1.2
2.1.7 HbA1c ≤ 12.0% (diabetic patients)
2.1.8 Subject or legal authorized representative must be willing to comply with the protocol including having blood drawn to create the RD1.
2.1.9 Female subjects who are capable of conceiving must use an acceptable form of contraception in order to participate in the study (acceptable forms of contraception include condoms for males and contraceptive pills or IUDs for women).

2.2. Exclusion Criteria

2.1.10 Presence of active underlying osteomyelitis.
2.1.11 Patient with a proven sepsis established by a blood culture in the past 2 weeks, or confirmed active infection likely to interfere with trial, such as urine tract infection
2.1.12 Known malignancy in the reference wound bed or margins of the wound
2.1.13 Exposure of blood vessels or organs at the base of the reference wound
2.1.14 History of alcohol or substance abuse, within the previous 2 months
2.1.15 Subject has participated in another clinical trial involving a device or a systemically administered investigational study drug or treatment within 30 days of day 0 visit.
2.1.16 Subject is currently receiving (i.e., within the past 30 days) or scheduled to receive a medication or treatment which, in the opinion of the Investigator, is known to interfere with, or affect the rate and quality of, wound healing (e.g., systemic steroids (more than 10mg per day), immunosuppressive therapy, autoimmune disease therapy, cytostatic therapy within the past 12 months, , radiation therapy to the ulcer area, vascular surgery, angioplasty or thrombolysis).
2.1.17 Subject has been treated with wound dressings that include growth factors, engineered tissues or skin substitutes (e.g., Regranex®, Dermagraft®, Apligraf®, GraftJacket®, OASIS®, Primatrix®, Matristem®, etc.) within 30 days of randomization or is scheduled to receive during the study.
2.1.18 Subject has been treated with hyperbaric oxygen within 5 days of screening or is scheduled to receive during the study.
2.1.19 Wound on a patient who has a life expectancy of less than 6 months.
2.1.20 Cannot withdraw blood in the required amount technically.
2.1.21 Known coagulation problems, abnormal thrombocytes level or if heparin is given intravenously. Patients who are taking orally Coumadin, Aspirin, or Plavix (clopidogrel) will not be excluded.
2.1.22 Hemoglobin anemia (< 9 g/dL).
2.1.23 Subject has an infectious disease, such as Acquired Immune Deficiency Disease (AIDS) or HIV, Hepatitis C, Hepatitis B, Human T-lymphotropic virus or Syphilis
2.1.24 Women who are pregnant or currently breast feeding.

2.3. Investigator and Site Selection

2.3.1 Investigators

Study investigator, will be instrumental in choosing the principal and co-investigators for the trial.

2.3.2 Sites Selection

All of the sites will have had training in Good Clinical Practices (GCP) with National Institutes of Health certification in the ethical treatment of human subjects.

3. DIAGNOSTIC EVALUATIONS

3.1. Laboratory Tests

HbA1c
Complete blood count
Coagulation tests – PT and PTT

4. STOPPING RULES

4.1. Individuals

4.1.1 Infection

An infection that cannot be controlled or interferes with treatment in such a way that a treatment failure is likely to occur.

If cellulitis or local wound infection occurs, the Investigator may interrupt treatment in order to address this adverse event. The Investigator will treat cellulitis or local wound infection in accordance with his clinical judgment. Systemic antibiotic therapy is permitted; however, topical antimicrobials are not permitted in combination with RD1. Investigator may interrupt treatment in order to apply topical antimicrobials and resume treatment later (in the time frame of 16 weeks only)

4.1.2 Venipuncture

Inability to complete a successful venipuncture resulting in complete loss of venous access.

4.1.3 Ulcer Deterioration

Ulcer deterioration, determined by physician discretion.

4.1.4 Health Deterioration

Any health deterioration or acute situation requiring hospitalization or likely to interfere with treatment and resulting in treatment failure.

4.1.5 Necrotic tissue:

Appearance of substantial necrotic tissue.

4.3. Study

4.2.1 ≥ 25% of ulcers have deteriorated (Ulcer deterioration is determined by physician discretion

4.2.2 ≥ 50% of ulcers have been infected.

4.2.3 ≥ 25% of patients have dropped out because of problems with venipuncture.

5. LONG TERM FOLLOW-UP

5.1. General

Following the 16-week study the subjects will be treated according to standard wound care. Subjects are kept in a database allowing follow-up studies to be conducted. Additional studies would only be performed with Ethics Committee approval and patient consent.

6. MISSED VISITS

If a subject misses a visit, the site is to make every effort to have the subject return as soon as possible to make-up the visit. Once the subject is seen, he/she is to return to his/her original visit schedule.

Patients who miss more than 2 two consecutive visits during the treatment phase will be withdrawn.

7. ADVERSE EVENTS

The NCI CTCAEv4 scale will be used to grade adverse events/serious adverse events.

7.1. Serious Adverse Events

Serious Adverse events (SAE) are defined as any adverse change in the subject's medical condition that meets any of the following criteria: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity (grades 3-5 using NCI CTCAEv4 scale).

Any serious adverse event that occurs during the subject's participation in the study, even though it may not be considered related to the study device by the Principal Investigator, must be reported on the case report forms. If an SAE is thought to be related to the device, it must also be catalogued under device-related adverse events.

SAEs are reported to the Institutional Review Board (IRB)/Ethics committee and the sponsor within 24 hours of recognition by the Principal Investigator.
Subjects who develop serious adverse effects should be followed until the event or effect resolves or stabilizes.

SAEs will be determined at each visit or whenever the site investigator is notified of an AE and determines it to be an SAE, and then recorded. The following information regarding SAEs will be collected:

- Description of the event
- Onset date
- Time of onset
- End date
- End Time
- Relationship to study device (e.g., yes, no, likely, unlikely)
- Action taken
- Outcome.

7.2. Device-related Adverse Events

Device-related Adverse Effects (DRAEs) are previously recognized or unrecognized adverse events directly related to the use of the RD1. These DRAEs will be reported to the IRB/EC and sponsor within 24 hours of the initial discovery of the event. They are also captured in the case report forms. A DRAE that is also determined to be an SAE will also be reported separately under SAE protocol.

Subjects who develop DRAEs should be followed until the event or effect resolves or stabilizes.

All DRAEs will be collected at each visit and recorded. The following information regarding AEs will be collected:

- Description of the event
- Onset date
- Time of onset
- End date
- End time
- Severity
- Categorization of event in relation to study device (Possible, Probable, Definite; Unrelated/Unlikely categories should be moved to the SAE/AE list).
- SAE (Y/N)
- Action taken
- Outcome.

Examples of incidents that might be DRAEs include, but are not limited to:

- Complications related to venipuncture but not including lack of venous access
- Infections appearing within 2-4 days of device application.
- Bleeding at the wound site that is not related to any debridement
- Any allergic reactions
- High pain related to product application or removal

7.3. Adverse Events

An adverse event (AE) is defined as any adverse change in the subject's medical condition including any deterioration, or exacerbation of a pre-existing medical condition that is observed by the Investigator or reported by the subject.

All AEs will be collected at each visit and recorded. The following information regarding AEs will be collected:

- Description of the event
- Onset date
- Time of onset
- End date
- End time
- Severity
- Action taken
- Outcome.

Examples of anticipated AEs include, but are not limited to:

- Infection not related to device application
- Increase in stage of wound
- Sudden increase in ulcer area or depth
- Peripheral edema or localized swelling
- New ulcer
- Systemic fever

7.4. Subject Referral to another Facility

In case a patient is referred to another facility during the course of the study treatment, due to and adverse event, **RD1 must be removed prior to subject referral and study treatment should be stopped**. In some cases, with sponsor approval, study treatment could be resumed following subject's return to the SNF.

8. PREMATURE WITHDRAWAL OF SUBJECTS

Subjects have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw a subject from the study, if he/she seems it to be in the subject’s best interest. It is recognized that an excessive rate of withdrawals may render the study uninterrupted and, therefore, it is desirable to avoid unnecessary withdrawals.

While lack of venous access is not anticipated as a major problem, a subject will be withdrawn from the trial if the investigator cannot find venous access during the treatment study visits (Visits 1-16).

Noncompliance with study treatment/ offloading in a manner that interrupt treatment and delay healing, according to principal investigator judgment

9. LOST TO FOLLOW-UP

Subjects who are lost to follow-up will be included in the primary safety analysis but only patients who complete the study will be included in the secondary objectives analysis; where wound area data are missing, imputation using LOCF (last observation carried forward) will be used.

10. SUBJECT COMPLIANCE

It is essential that patients comply with the protocol. The Principal Investigator should make every effort to ensure patient compliance.

11. STUDY MONITORING

11.1. Study Records/Source Document Inspection

The data for subjects will collected on case report forms (CRFs) and kept in a secure location in accordance with HIPAA regulations. The site investigator will allow the research team (nurses, data managers etc.), representatives of the sponsor, its monitoring team, the local IRB/EC, and other governmental regulatory agencies to monitor/audit/inspect all study records, CRFs, IRB/EC/IEC records, and corresponding portions of the site investigator's office and/or hospital medical records at regular intervals throughout the study. These monitoring/audits/inspections are conducted to verify adherence to the protocol, integrity of the data being captured on the CRFs, and compliance with applicable regulations. The sponsor requires that subjects' medical records will be maintained in a confidential manner. Study reports will not identify subjects by name or other identifiers.

11.2. Monitors

Each study site will be monitored by a qualified representative of the sponsor or any qualified monitor delegated to do so, on behalf of the sponsor. The monitor will scrutinize study data and conduct at regular intervals throughout the course of the study according to a pre-defined monitoring plan. On-site monitoring of the site investigator's facilities aids in ensuring compliance with the protocol.

Any deficiency noted during the monitoring visits will be discussed with the site investigator and corrective actions to be taken agreed upon. Should the sponsor determine at any time during the study that the site investigator is not in regulatory and/or protocol compliance, measures necessary to establish compliance will be implemented. If compliance cannot be maintained, the sponsor will suspend or terminate the study at this site.

11.3. Monitoring Plan

11.3.1 Pre-study visit

1. Assess the site's infrastructure (staff and facility) for the capability to conduct the study.
2. Evaluate Investigator and staff member's experience, qualifications, and capabilities; signed and dated CVs.
3. Financial disclosure information.

The sponsor may waive the pre-study visit in certain sites based on previous knowledge or experience with the site or personnel, or other reasons as deemed acceptable.

11.3.2 Study initiation visit

Orient the site investigator's staff involved in the study on:

1. Protocol content and procedures
2. CRF and fill-in process, including queries resolution process
3. GCP and other regulatory requirements
4. Informed consent form and process
5. AE, SAE, DRAE, safety reporting
6. IRB/EC
7. Investigational product accountability
8. Subject information: subject's identification log, subject pre-screening and screening logs, subject enrollment log, and subject study visit log
9. Study monitoring
10. Investigator's site file (ISF)
11. Report of AEs back from the sponsor to the sites (expedited safety reports)
12. Expectations from the site regarding data collection and timelines

The sponsor may choose to perform a regional investigator meeting instead of the initiation visits at each site.

11.3.3 Regular monitoring visit

1. Check on the progress of the study
2. Protocol and GCP compliance
3. Informed consent form and process
4. CRF completion, correction, source data verification
5. AE, SAE, DRAE, safety reporting
6. Investigational product
7. Investigator's study file.

(Detailed monitoring schedule to be provided at study initiation.)

11.3.4. Intermediate and final study visit; close out monitoring visit

Ensure Investigator understands the ongoing responsibilities

1. Record archival practices for source documents and CRFs after completion of the study—up to 15 years.
2. Follow-up of ongoing DRAEs—up to 30 days after completion of the study and of SAEs—until resolution.
3. Notify the sponsor in the event of Health Authority inspection.
4. Finalizing all "open" issues and complete source data verification (SDV).

12. RECORDS HANDLING AND KEEPING

12.1. Source Documents

Source documents are the initial documents in which subject data are recorded. This includes, but is not limited to, original subject files, hospital records, and original recordings/tracings from automated instruments, etc.

The sponsor allows using dedicated work sheets to serve as source documents to collect the available source data, on top of all other applicable source documents in the site.

All information captured on the CRF should be accurately supported by the source documents unless specifically approved and documented by Sponsor. For example, each subject's source documents should include (but not be limited to):

- Documenting the informed consent process
- Subject full name and identification
- Date of each study-required visit with a description of the visit and the results of each procedure that was performed
- A full and comprehensive anamnesis that will cover subject's medical history, current disease, etc.
- All concomitant procedures and medications for the screening eligibility purposes and regular visits

Any additional information relevant to the study should be included in the subject's source documents. In particular, any deviations from the study protocol or procedures should be recorded in the source documents, if noted. For example, if study-required procedures or visits are not completed or are completed outside the time frame specified in the protocol, the reasons for the departure should be explained in the source documents, or mentioned whether it was waived by the sponsor in advance. The investigator must maintain all study documentation at least 2 years after the last approval of marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. The sponsor should inform the investigator in writing when the trial-related records are no longer needed.

All study personnel will receive training in protecting the confidentiality of study participants and their health information. Study personnel will be asked to provide written verification of their receipt of the training. Study data will be coded with a study specific code and will not contain participant names. Informed consent forms and other documents that include names or linkages between study numbers and names will be kept in a secure locked manner with limited access. All databases will be password protected to limit unauthorized access to study data.

12.2. Data Collection Method

Data from the subject's permanent medical records (see source documentation section) will be recorded on CRFs. These CRFs will be used to transmit the information collected in the performance of this study to the clinical database either manually or by electronically.

All source data must be typewritten or filled out in ballpoint pens, accurately and promptly following each visit. The corresponding CRF should be completed so that no fields are left blank. CRFs entries corrections will be made only by crossing out (single line) incorrect data and writing in the revisions. All corrections must be initialed and dated by the individual performing/recording them. If the reason for the change is not obvious, an explanation will be recorded. Blacking out or using correction fluid or an eraser is not allowed to eliminate data. The investigator must review the CRFs for completeness and accuracy and must sign/date the forms where indicated. Signature stamps or substitutes are not acceptable. The investigator will retain originals of all source documents, subject consent forms, and study data as a permanent record.

Each set of CRFs copy should be reviewed for accuracy and completion (signatures, dates, adverse events, device-related adverse events, serious adverse events, protocol departures) and maintained in the investigator's study site.

All original data, both paper forms and electronic, will be kept in a secure place with limited access; these will be kept in secure locked cupboards at the site. Electronic files will be password protected and kept on a study computer or server to which only the study coordinator, personnel, and PIs will have access.

13. DATA ANALYSIS

13.1. Study Population and Sample size

13.1.1 The safety population will be all subjects who receive at least one RD1 treatment.

13.1.2 The intent-to-treat population (ITT) will be all subjects who complete the study.

13.1.3 Sample size is initially set as 60 but enrollment will be increased if necessary to compensate for drop-outs so that 60 patients complete the trial.

13.2. Statistical Analyses

Please refer to the SAP (statistical analysis plan) for full details.

13.2.1. Primary Endpoint

Efficacy- The performance of RD1 in terms of wound progress towards closure in wounds deemed suitable for treatment with RD1 (ITT population)

13.2.2. Secondary Endpoints

- Safety - Determine complication rates for all adverse events compromising serious adverse events, adverse events (AEs), and device-related adverse events (DRAEs); AEs include any lack of venous access events (ITT and Safety Population)
- Efficacy - Assess the incidence of complete wound closure at 16 weeks for wounds treated with RD1 (defined as skin re-epithelialization without drainage or dressing requirements) (ITT population).
- Efficacy - Assess the wound Percent Area Reduction (PAR) (ITT population)
- Efficacy- Assess the optimal duration between applications of RD1 per wound parameter (ITT population)
- Efficacy- Assess the need of design and procedure improvements of the RD1 for specialized nursing facilities (SNF) (ITT population)
- Sub Group Analysis – asses the safety and efficacy per wound etiology (subgroup of ITT population)
- Asses the cost of RD1 procedure in SNF compared to cost of treatment before RD1 (ITT population)
- Assess wound pain compared to wound pain during treatment before RD1 (ITT population)
- Assess medical staff wound related weekly labor of wound treatment before and during RD1. (ITT population)

14. REGULATORY OBLIGATIONS

14.1 Sponsor's Obligations

The sponsor will assume the following responsibilities:

1. Provide the investigator with the necessary information—protocol and device user's manual or instructions for use (also incorporated into the Investigator Brochure).
2. Inform the Investigator of all new information that may affect his/her decision of whether to continue participation in the study.
3. Provide supplies for the investigation.

The sponsor will maintain the following records:

1. A signed protocol and CRF
2. All correspondence that relates to the clinical trial
3. Signed investigator agreements
4. Records of device shipment and disposal (shipping receipts, material destruction records, etc.)
5. Other records as required by the Health Authority.

14.2 Investigator's Obligations

Clinical research studies are subject to the regulations of the regulatory authority of the country. Upon signing the protocol, the investigator agrees to assume the following responsibilities and to keep the required records for a period of 2 years after the last approval of marketing application and until there are no pending or contemplated marketing

applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, and to file the required reports in a timely manner:

1. Conduct the investigation in compliance with the protocol. Changes to the protocol may only be made after approval by the investigation team and the Ethical Committee (IRB/EC), or when necessary to protect the safety, rights, or welfare of a subject.
2. Personally conduct or supervise the investigation.
3. Read and understand the information in the Protocol and Investigator Brochure.
4. Be aware of the potential risks and side effects of the investigational device.
5. Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations.
6. Inform all subjects that the device is being used for investigational purposes and ensure that the requirements related to obtaining the informed consent are met.
7. Dispose of or return remaining supplies as directed by the sponsor.
   Maintain the following records (for the period of time as specified above):
   1. Signed copy of the protocol
   2. Signed consent forms
   3. All correspondence relating to the clinical trial
   4. Case Report Forms.

File the following reports:

1. Serious unexpected adverse DRAE reports received by the sponsor.
2. Regular SAE reports produced by the PI.
3. Deviations made from the protocol for emergency use, must be reported to the sponsor as soon as possible, but no later than five working days after occurrence.

15. STUDY COMPLETION

The PI will complete and report the study in satisfactory compliance with the protocol.
It is agreed that, for any reasonable cause, either the PI or the Sponsor, may terminate this study, provided a written notice is submitted at a reasonable time in advance of intended termination. If the study is terminated for safety reasons, the investigator will be notified immediately by telephone, followed by written instructions for study termination notification of the IRB/EC.

16. PROTOCOL DEVIATIONS AND EXCEPTIONS

The investigator should not implement any deviation from or changes to the protocol without agreement of the sponsor, in some cases the IRB/EC should be notified and approve the deviation (if safety to the subject or if the scientific soundness of the study is involved), except where necessary to eliminate an immediate hazard(s) to trial subjects.

The investigator should document and explain any deviation from the approved protocol and file waivers received from the sponsor, if applicable. The reasons, and if appropriate, the proposed protocol amendments should be documented in the CRF and submitted to:

1. The sponsor for agreement
2. IRB/EC
3. The regulatory authority.

17. ETHICAL STUDY CONDUCT

This study will be conducted in compliance with the protocol after approval of the IRB/EC, and according to Good Clinical Practice (GCP) and international standards, such as ISO 14155. No deviation from the protocol, after the investigation team approval will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB and to the sponsor as soon as possible.

A copy of the protocol, Informed Consent Form (ICF), and advertising material must be submitted to the IRB/EC. Written approval of the protocol ICF and advertising material must be obtained prior to subject enrollment by the IRB/EC.

18. CONFIDENTIALITY/PUBLICATION OF STUDY RESULTS

This clinical study is confidential and should not be discussed with individuals outside the study. Additionally, the information in this document and in the study may contain secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study that have a need to know, but all such persons must be instructed not to further disseminate this information to others.

For publication rules please see the agreed upon signed study contract with the study center.

The data may be used now and in the future for presentation or publication at the investigator and/or sponsor's discretion or for submission to governmental regulatory agencies. All reports and communications relating to subjects in the study will identify each subject only by the subject's initials and by the subject's study number.

APPENDIX 1
INFORMED CONSENT FORM

APPENDIX 2
RD1™ APPLICATION PROTOCOL

RD1 Preparation

The patient phlebotomy kit includes the following products:

- 1 Sterile syringes of 2.5 mL;
- A sterile syringe of 20 mL;
- A CPDA1 blood collection bag (as a source of CPDA1 anti-coagulant) or two FDA cleared vacuum tubes with ACDA Solution
- A sterile blood collection set with a 21G needle

The coagulation initiator and accelerator kit includes the following items:

- A 10 mL sterile ampoule of calcium gluconate (manufactured by APP Pharmaceuticals);
- 35 mg kaolin powder (manufactured by Charles B. Chrystal Co., Inc.), sterilized in a vial; and
- A 10 mL syringe.

The clotting trays consist of 3 sizes of sterile biocompatible plastic boxes, each containing sterile cotton medical gauze. The trays are separately packed and marked small, medium or large, with the RD1 diameter written on them. The sizes of the clotting tray (small, medium or large) to be used to create RD1 patches for different wound sizes are also presented in **Table 1** below.

Table 1. Clotting trays.

Clotting tray	**Picture**	**RD1 diameter**
Small		2.8 cm
Medium		3.7 cm

Large		4.5 cm

Follow the instructions below to use the RD1 System:

1. Measure the ulcer maximal length.
2. Open the sterile RD1 kit, and spread its contents on a flat, sterile surface near the patient.
3. Select the appropriate clotting tray size based on the measured maximal wound size, and place it in the empty kit tray.
4. Make sure that the RD1 tray cover is firmly attached to the tray from all sides so blood will not leak.
5. Make sure the RD1 tray is horizontal.
6. Use the materials titration table and the steps described below to create the RD1 whole blood clot gel:

Table 2. Materials titration table.

RD1 Clotting Tray	**Procedure Syringe**	**CPDA1 Anti-coagulant**	**Blood Amount**	**Coagulants Mixture 6 mL Calcium in Kaolin Vial**	**Final Volume in syringe**	**Amount to be injected to RD1 clotting tray**	**RD1 Circular Area Covered**
Small	20 mL	1 mL	10 mL	2 mL	13 mL	7 mL	8.8 cm^2
Medium	20 mL	1 mL	10 mL	2 mL	13 mL	10 mL	11.6 cm^2
Large	20 mL	1 mL	10 mL	2 mL	13 mL	13 mL	16 cm^2

7. Preparing the CPDA1 in a syringe or the ACDA tubes

In case of CPDA1 syringe:

a. Insert the needle of the 2.5 mL syringe into the bag containing CPDA1
b. Withdraw CPDA1 in the amount specified in Table 2.
c. Inject the CPDA1 from the 2.5 mL syringe into the 20 mL procedure syringe.
d. Cover the procedure syringe with a covered needle.

In case of ACDA tube

e. Extract the tube from the kit

8. Preparing coagulants mixture (6 mL calcium gluconate in the kaolin vial):

a. Withdraw 6 mL calcium gluconate from its ampoule, using the 10 mL syringe with a needle.
b. Inject the 6 mL calcium gluconate into the sterile sealed kaolin powder glass vial through its rubber plug, and close the needle cover.
c. Shake the kaolin and calcium gluconate mixture well until a uniform suspension is obtained.
d. Remove the needle cover and withdrawal the calcium + kaolin suspension into the 10 mL syringe, according to the amount in Table 2.

9. Phlebotomy:

a. Change the needle to a new one on the 20 mL syringe containing the CPDA1.
b. Wrap tourniquet proximal to the puncture site.
c. Cleanse venipuncture site with alcohol prep.
d. Withdraw blood from the patient vain in the appropriate amount, according to Table 2, using the blood collection set 21G needle, either with CPDA1 syringe or 2 ACDA 8.5ml tubes.
e. Remove the tourniquet and the needle
f. Apply pressure to the site with 2" x 2" gauze. Apply a band-aid over the site.
g. Introduce a small amount of air into the syringe in order to facilitate the mixing of the syringe contents. Tilt the syringe gently 3-4 times or tilt the tubes.

Note – Blood withdrawal and handling should be performed according to standard blood withdrawal precaution guidelines.

10. In case you used 2 vacuum tubes: draw 12ml of the tube content into the 20ml syringe and dispose of the 2 tubes
11. Inject the calcium + kaolin suspension from its syringe into the 20 mL syringe containing the blood.
12. Draw some air into the syringe in order to facilitate the mixing of the syringe contents. Tilt the syringe gently 3-4 times.
13. Remove the needle to prepare for injecting the material into the RD1 clotting tray, which must be done immediately.
14. Insert the syringe tip into the upper hole in the RD1 tray.
15. Inject the coagulating blood into the RD1 tray using moderate pressure, as shown below.

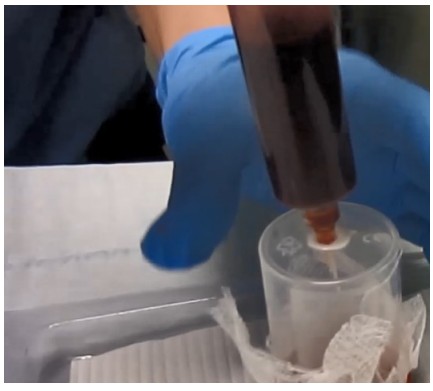


Figure 1. Immediate injection into the RD1 tray.

16. Wait 12 minutes for complete coagulation to occur.
17. Use one hand to affix the pad rim and clotting tray base while the other hand lifts the lid of the tray.
    For the medium and small clotting trays: Use one hand to hold the clotting tray while the other hand affixes the pad rim on the lid, and screw out both gauze and lid (see Figure 2).

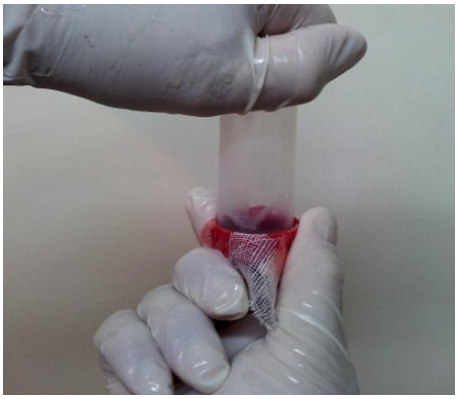


Figure 2. Opening the clotting trays.

Handling and placing the RD1:

18. Wear sterile gloves.
19. Gently remove the RD1 from the clotting tray by holding it from its rim. Use both hands.
20. Place the RD1 over the wound with the embedded pad facing upwards (distal).
21. The RD1 clot gel may be shaped, if needed, by cutting it with sterile scissors. Cutting should be performed on the surgery tray or while being held in the gloved hand.

Note: Make sure that the RD1 is large enough to cover the entire wound, covering at least 0.5 cm of surrounding skin around wound edges.

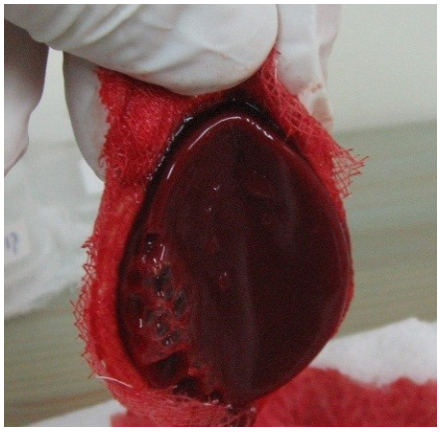


Figure 3. Handling the RD1.

Affixing the RD1:

22. Anchor the RD1 to the wound by its rim with Steri-strips.
23. Place a primary non-adhesive dressing such as Mepitel over the RD1.
24. Place a secondary absorbent dressing on top.

RD1 Removal (after approx. 7 days):

25. Wear gloves.
26. Remove the remaining RD1 by pulling it gently off the wound.
27. In case of adhesions, wet the RD1 with saline to facilitate gentle removal.
28. Discard of the remaining RD1 properly.

RD1 kit allocation

RedDress ltd. Will provide the research centers pharmacies/ designated personnel with the RD1 investigational kit. The pharmacies/ designated personnel will allocate the supply to the investigators, in accordance to a pre-defined procedure.

RD1 kit storage conditions

Store in the original container at a controlled room temperature of 15°C (59°F) – 25°C (77°F). Protect from freezing and avoid excessive heat.

Shelf Life

2 Years from date of manufacturing

Disposal instructions

Dispose of all blood, tools, and materials according to local requirements.

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

APPENDIX 3
PHOTOGRAPHIC TECHNIQUE

3 Photographs will be taken at every visit:

1. Before RD1 removal (not relevant for screening visit and day 0 visit)
2. Before cleansing and debridement (if performed)
3. After cleansing and debridement- before RD1 application.

All research staff must undergo training for the use of the specifically designated camera that is used in the standard work, including:

1. Specific photography guidelines as, lightning, distance from ulcer and direction of photography
2. Performing 2 photos per ulcer
3. Validating the quality of the photo
4. Allocating specific name to the photo file
5. Saving photos
6. Sharing photos
7. Measuring the ulcer in the photo
8. Measuring the depth of the ulcer
9. Backup of photos

APPENDIX 4
WOUND MEASUREMENT

Wound size measurements will be obtained using digital analysis with acceptable tool, before the use of the tool validation data will be assessed and the tool will be cleared for use by sponsor.

Wound depth measurement will be obtained by an accepted method, i.e. Measure distance from deepest base of wound bed to level of usual skin surface and at a 90° angle to skin surface using a sterile probe and ruler. Unit of measurement is millimeters.

APPENDIX 5
IMAGING CHARTER

The main goal of central imaging/planimetry review is to confirm assessment by an additional assessor that a wound has closed (initial assessment, then re-assessment 2 weeks later). Secondary goals include confirming each wound eligibility at study entry, review of a wound that has increased ≥ 50% in area or increased in grade to confirm whether a patient should be withdrawn, or review at the request of any site assessor.

The following steps will occur:
1. There will be one independent central reviewer who is experienced at wound care.
2. The reviewer will receive the wound image and data via e-mail
3. The reviewer will assess whether the wound is closed or not (or other assessment, as requested).
4. The reviewer will communicate his or her decision to the Medical Monitor.
5. If there is disagreement between the site assessor and the imaging reviewer, then the Medical Monitor will adjudicate using best judgment, and communicate any change in wound status back to the site assessor. The Medical Monitor will also have access to wound images and data from patient visit records.

APPENDIX 6
TRAINING AND STANDARDIZATION OF CARE AT CENTERS

All study personnel will be trained in the care of ulcers and specific procedures as noted below:

Centers will follow debridement techniques according to appendix 8 of this protocol.
Centers will follow photography techniques according to appendix 3 of this protocol
Centers will follow infection assessments technique according to appendix 11 of this protocol
Centers will follow moisture control assessments technique according to appendix 12 of this protocol
Centers will follow offloading techniques according to appendix 13 of this protocol
Centers will follow wound grading system according to appendix 9 of this protocol

APPENDIX 7
SCHEDULE OF EVENTS

PROCEDURES	SCREENING PHASE (DAY 0)	RD1 CHANGE ASSESSMENT VISIT	RD1 RE-APPLICATION VISIT	HEALING CONFIRMATORY VISIT (if applicable)	END OF STUDY/ EARLY TERMINATON VISIT
Informed Consent	X				
Inclusion/Exclusion	X				
Medical History	X				
Physical Exam	X			X	X
Demographics	X				
Ulcer classification and grading	X				
Neuropathic assessment (Foot Ulcers only)	X				
Infection assessment	X	X	X	X	X
Assessment of moisture control	X	X	X	X	X
Vascular perfusion assessments (when relevant)	X				
Laboratory tests	X			X	X
X-Ray of the study ulcer	X (only if osteomyelit is suspected)				
Ulcer and blood related concomitant Meds	X	X	X	X	X
Standard of care therapy	X				
Ulcer cleansing and debridement	X		X		X
RD1 change assessment		X			
Apply RD1	X (day 0 only)		X		
Wound photography	X	X	X	X	X
Wound measurement/assessment	X	X	X	X	X
Adverse Event	X	X	X	X	X
Offloading Compliance Assessment	X	X	X	X	X
Pain Assessment	X		X	X	X
Staff labor assessment	X		X	X	X
Pre-RD1 wound treatment cost assessment	X (on screening)				
RD1 procedure cost assessment	X (on day 0)			X	X

APPENDIX 8
DEBRIDEMENT

Debridement is an essential technique in the treatment of chronic ulcers. It is important to remove all non-viable and necrotic material from the target ulcer prior to enrolling the patient. It is also important that that all of the investigators debride the wound in a similar fashion. The study site will be provided with a training video and all of the investigators will be trained on the technique. Briefly, the following procedures should be followed:

1. The target ulcer and the surrounding skin are prepped with saline solution.
2. Using clean technique a surgical blade and/or scissors and forceps the skin around the edge of the wound is excised. All non-viable and necrotic tissue in the wound bed is removed.
3. Ideally hemostasis is achieved using direct pressure. Cautery may be employed if necessary, but should not be done more than once.

APPENDIX 9
ULCER GRADING SYSTEM

Each wound will be classified and graded according to the relevant etiology grading system, as described below:

Pressure Ulcers

Pressure Ulcer Stages Revised by NPUAP

Suspected Deep Tissue Injury:
Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue.

Further description:
Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed. The wound may further evolve and become covered by thin eschar. Evolution may be rapid exposing additional layers of tissue even with optimal treatment.

Stage I:
Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area.

Further description:
The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Stage I may be difficult to detect in individuals with dark skin tones. May indicate "at risk" persons (a heralding sign of risk)

Stage II:
Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled blister.

Further description:
Presents as a shiny or dry shallow ulcer without slough or bruising.* This stage should not be used to describe skin tears, tape burns, perineal dermatitis, maceration or excoriation.
*Bruising indicates suspected deep tissue injury

Stage III:
Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.

Further description:
The depth of a stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and stage III ulcers can be shallow. In contrast, areas of

significant adiposity can develop extremely deep stage III pressure ulcers. Bone/tendon is not visible or directly palpable.

Stage IV:
Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunneling.

Further description:
The depth of a stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and these ulcers can be shallow. Stage IV ulcers can extend into muscle and/or supporting structures (e.g., fascia, tendon or joint capsule) making osteomyelitis possible. Exposed bone/tendon is visible or directly palpable.

Unstageable:
Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green or brown) and/or eschar (tan, brown or black) in the wound bed.

Further description:
Until enough slough and/or eschar is removed to expose the base of the wound, the true depth, and therefore stage, cannot be determined. Stable (dry, adherent, intact without erythema or fluctuance) eschar on the heels serves as "the body's natural (biological) cover" and should not be removed.

For more information, contact npuap.org or 202-521-6789

Diabetic Foot Ulcers

Wagner grade

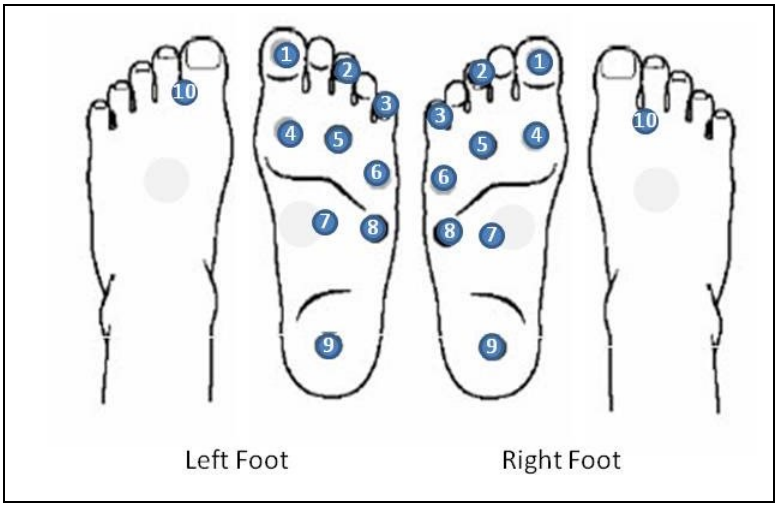
Grade 0- No open lesions; may have deformity or cellulitis
Grade 1- Superficial diabetic ulcer (partial or full thickness)
Grade 2- Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
Grade 3- Deep ulcer with abscess, osteomyelitis, or joint sepsis
Grade 4- Gangrene localized to portion of forefoot or heel
Grade 5- Extensive gangrenous involvement of the entire foot

APPENDIX 10
NEUROPATHIC ASSESSMENT

Neuropathic Assessment- foot ulcers only

Sensory neuropathy will be quantified using the Semmes-Weinstein test to evaluate the 10 locations shown in Figure 1. For this trial, the 10 g 5.07 gauge monofilament will be used. The number of sites where the subject does not perceive sensation will be recorded in the CRF.

Figure 1. Semmes-Weinstein 10 Point Sensory Neuropathy Screen



APPENDIX 11
INFECTION ASSESSMENT

Infection of the index wound will be determined by the physician, taking into account the following parameters:

1. Increased surface area, depth or grade.
2. Increased periwound margin temperature by more than 3^{o}F difference between 2 mirror image sites;
3. New areas of breakdown or satellite lesions
4. Presence of swelling or reddened skin in periwound area
5. Increased wound drainage
6. Unpleasant, sweet, or sickening odor present.
7. Excessive bleeding on a wound
8. Increased pain of the wound

In the case the wound has exposed bone or can be probed to the bone, the patient will be withdrawn from the study.

APPENDIX 12
MOISTURE CONTROL ASSESSMENT

Assessment of moisture control will be based upon determining whether there is maceration at the skin edge. If there is maceration, clinicians will be instructed to examine whether the secondary absorbent dressing is appropriate, or whether excessive exudation is taking place. The clinician may also elicit discussion with the patient regarding care of the wound.

APPENDIX 13
OFFLOADING DEVICE INSTRUCTIONS

Offloading will be assessed at each visit and determined whether it is adequate, and whether patient compliance is satisfactory. Because there is little evidence to suggest that one type of offloading is superior to another, if a pressure-relieving surface is being utilized for a truncal ulcer (such as an appropriate overlay or alternating/low-air-loss mattresses for full-thickness ulcers), appropriate footwear for a heel ulcer (active offloading walker (boot and/or shoe)), or suitable pressure relief for any other ulcer location, then offloading will be regarded as adequate. If this is not the case, the patient will be further educated.

For subjects who do achieve complete closure during the treatment phase, use of the offloading device is recommended for at least 2 weeks.

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APPENDIX 14
STANDARD CARE

The study center will provide the study ulcer with standard care during screening period, per physician discretion

APPENDIX 15
INVESIGATOR SUBJECTIVE ULCER PAIN ASSESSMENT

Investigator will assess the ulcer pain level of the subject, from 0 to 10, based on observation on the subject prior to RD1 removal.

APPENDIX 16
PROCEDURE COST AND STAFF LABOR ASSESSMENTS

Staff labor (human resource) and procedure cost data will be gathered during the study including also subject and medical staff questionnaires. Specific parameters will be determined after the first 5 subject will complete the.

INVESTIGATOR AGREEMENT FOR TRIAL PROTOCOL

I have read the foregoing protocol RD004, and agree to:

- Conduct the study as outlined herein;
- Maintain the confidentiality of all information received or developed in connection with this protocol, and
- Conduct this study in accordance with GCP standards and any other applicable local/state laws and regulations;
- Comply with the signed investigators agreement.

_____ _____

Investigator Signature **Date**

_____

Investigator name in capital letters

_____

Telephone number

_____

Fax number

_____

Email address

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