A Prospective, Randomized, Comparative Effectiveness Study of a Single-Use, Negative Pressure Wound Therapy System (PICO) versus a Traditional Negative Pressure Wound Therapy System (tNPWT) in the Treatment of Lower Extremity Ulcers

Protocol Number:	CE/052/PIC
Sponsor Name & Address:	Smith & Nephew, Inc. 3909 Hulen Street, Fort Worth, Texas 76107
Test and Control Article(s):	PICO - Single-Use Negative Pressure Wound Therapy (NPWT) System, Smith & Nephew, Inc., Fort Worth, TX. ActiV.A.C.® Negative Pressure Wound Therapy (NPWT) System, Kinetic Concepts, Inc., (KCI) an Acelity Company, San Antonio, TX. Invia® Liberty Negative Pressure Wound Therapy (NPWT) System, Medela, Inc., McHenry, IL. Avance® Negative Pressure Wound Therapy (NPWT) System, Mölnlycke Health Care, Göteborg, Sweden Renasys◊ Negative Pressure Wound Therapy (NPWT) System, Smith & Nephew, Inc., Fort Worth, TX. – For use only in countries where clearance from the appropriate regulatory authorities has been received
Protocol Version	(1.0, Original Issue, 08 May 2015)

(2.0, Incorporating Amendment 1, 12 June 2015)

(3.0, Incorporating Amendment 2, 23 February 2016)

(4.0 Incorporating Amendment 3, 5 April 2016)

(5.0 Incorporating Amendment 4, 22 August 2016)

1.1 INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Prospective, Randomized, Comparative Effectiveness Study of a Single-Use, Negative Pressure Wound Therapy System (PICO) versus a Traditional Negative Pressure Wound Therapy System (tNPWT) in the Treatment of Lower Extremity Ulcers", dated **22 August 2016**, and agree to abide by all provisions set forth therein.

I agree to comply with the Investigator Obligations stipulated in Section 18.12 of the protocol.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the described clinical investigation without the prior written consent of Smith & Nephew, Inc.

_____

Signature

_____ _____

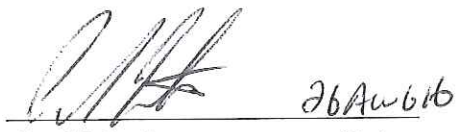
Name of Principal Investigator (print) Date

1.2 SPONSOR APPROVAL

A Weymann 8/25/16

A Weymann 8/25/16	Jaime E Dickerson 25 AUG 2016
Andy Weymann, MD Date	Jaime E. Dickerson, PhD Date
Senior Vice President & Chief Medical Officer	Vice President, Global Clinical Operations
25 Aug 2016	D. Innes Cargill 25 Aug 2016
Alan Rossington, MEng, MSc Date	D. Innes Cargill, PhD Date
Director Biostatistics and Data Management, Global Clinical Operations	Medical Monitor Director, Global Clinical Operations and Medical Monitor
RJ Eichelkraut 25 AUG 2016	Bobbi Drais 24 AUG 2016
Robert Eichelkraut, MBA Date	Bobbi Drais Date
Senior Director, Global Clinical Operations	Vice President, Regulatory Affairs

1.3 SPONSOR REVIEW



26 Aug 16

Paul Martin Date

Sr. Manager, Quality Assurance

1.2 SPONSOR APPROVAL

Andy Weymann, MD	Date
Senior Vice President & Chief Medical Officer	

Jaime E. Dickerson, PhD	Date
Vice President, Global Clinical Operations	

Alan Rossington, MEng, MSc	Date 25 Aug 2016
Director Biostatistics and Data Management, Global Clinical Operations	

D. Innes Cargill, PhD	Date 25 Aug 2016
Medical Monitor Director, Global Clinical Operations and Medical Monitor	

Robert Eichelkraut, MBA	Date 25 Aug 2016
Senior Director, Global Clinical Operations	

Bobbi Drais	Date 24 AUG 2016
Vice President, Regulatory Affairs	

1.2 SPONSOR APPROVAL

A Weymann 8/25/16		for Jaime E Dickerson 25 AUG 2016	
Andy Weymann, MD	Date	Jaime E. Dickerson, PhD	Date
Senior Vice President & Chief Medical Officer		Vice President, Global Clinical Operations	
25 Aug 2016		D. Innes Cargill 25 Aug 2016	
Alan Rossington, MEng, MSc	Date	D. Innes Cargill, PhD	Date
Director Biostatistics and Data Management, Global Clinical Operations		Medical Monitor Director, Global Clinical Operations and Medical Monitor	
RJ Eichelkraut 25 Aug 2016		Bobbi Drais 24 AUG 2016	
Robert Eichelkraut, MBA	Date	Bobbi Drais	Date
Senior Director, Global Clinical Operations		Vice President, Regulatory Affairs	

1.2 SPONSOR APPROVAL

Andy Weymann, MD Senior Vice President & Chief Medical Officer	Date
Jaime E. Dickerson, PhD Vice President, Global Clinical Operations	Date
Alan Rossington, MEng, MSc Director Biostatistics and Data Management, Global Clinical Operations	25 Aug 2016 Date
D. Innes Cargill, PhD Medical Monitor Director, Global Clinical Operations and Medical Monitor	Date
Robert Eichelkraut, MBA Senior Director, Global Clinical Operations	Date
Bobbi Drais Vice President, Regulatory Affairs	24 AUG 2016 Date

1.3 SPONSOR REVIEW

Paul Martin Date

Sr. Manager, Quality Assurance

1.3 SPONSOR REVIEW

26 Aug 16

Paul Martin Date

Sr. Manager, Quality Assurance

2. SYNOPSIS

Study Phase	4
Financial Disclosure Information to be Obtained?	☐ Yes ☑ No
Test Article(s) / Products:	Single-Use Negative Pressure Wound Therapy (PICO) System Traditional Negative Pressure Wound Therapy (tNPWT) System
Study Dosage / Usage:	PICO - Negative Pressure Wound Therapy (NPWT) at -80 mmHg (nominal) +/- 20 mmHg to the wound surface tNPWT in the range of -40 mmHg and up to -200 mmHg; intensity settings of either low, medium and high; delivery modes of continuous or intermittent. The pressure, intensity and delivery settings will be left to the Investigator's discretion at each study treatment visit. (See appendix 18.11 for examples of appropriate devices).
Active Ingredients:	NA
Route of Administration:	Wound Dressing

Objective(s):

PRIMARY: To compare PICO against tNPWT for the percentage change in the target ulcer area over the 12-week treatment period from baseline

KEY SECONDARY: To compare PICO against tNPWT for the percentage change in the target ulcer depth and volume over the 12-week treatment period from baseline

SECONDARY:
(1) To compare PICO against tNPWT in the time (days) to achieve confirmed complete target ulcer closure by either surgical intervention or secondary intention
(2) To compare PICO against tNPWT for the proportion of subjects that achieve confirmed complete target ulcer closure by either surgical intervention or secondary intention
(3) To compare PICO against tNPWT for differences in Health Related Quality of Life (HRQoL) over the 12-week treatment period

EXPLORATORY: Assessment of a difference in the following target ulcer assessments over the 12-week treatment period and to compare PICO against tNPWT:

- Condition of the target ulcer peri-wound skin
- Estimation of tissue types present on the target ulcer
- Clinical signs and symptoms of infection on the target ulcer
- Incidence of target ulcer infection
- Pain on removal of dressing
- Pain on initiation of therapy/during dressing wear
- Dressing wear time
- Additional interventions
- Impact of the device on aspects of daily living and satisfaction with device therapy

SAFETY: Adverse events associated with the target ulcer and all AE judged to be serious (SAE) will be recorded.

Study Population:	Adults, 18 years of age and older, presenting with lower extremity ulcers between ≥ 2.0 cm^2 and ≤ 36.0 cm^2 in area, and < 15 cm in one linear direction for VLU, and between ≥ 0.5 cm^2 and ≤ 10 cm^2 for DFU, ≥ 4 weeks and ≤ 104 weeks in duration for VLU and ≥ 4 weeks and $\leq$ 52 weeks in duration for DFU.		
Structure:	☑ Parallel Group	Duration of Treatment:	Up to 12 weeks
		Duration of Assessment:	Up to 14 weeks
	☐ Crossover	Number of Treatments:	N/A
		Number of Sequences:	N/A
		Number of Periods:	N/A
		Duration of Periods:	N/A
		Washout Between Periods:	N/A
	☐ Other	N/A	
		Duration of Treatment	N/A
Multi-Center:	☑ Yes	Number of Centers: Approximately 15 sites (plus replacements, if needed)	
	☐ No		
Blinding:	☑ None		
	☐ Observer-Blind		
	☐ Subject-Blind		
	☐ Double-Blind		

Randomization:	✓	Yes	Group Assignment Ratio:1:1 Treatment will be randomized, stratified by wound type and wound size to prevent imbalance on these variables between the two treatment groups. The resulting strata will be as follows: Small DFU (≤2 cm^2), large DFU (>2 cm^2), small VLU (≤12 cm^2) and large VLU (>12 cm^2)
		No	

Concurrent Control:		None	
		No Treatment	
		Placebo	Specify: NA
	✓	Active	Specify: tNPWT
		Other	Specify: NA

Estimated Total Sample Size:	Approximately 160 subjects will be enrolled to ensure that at least 128 subjects complete the study. A minimum of 100 VLU and 46 DFU will be enrolled; there will be no stipulation on wound type for the remaining subjects. An interim analysis will be performed after approximately 80 subjects have completed the study, including a minimum of 40 VLU and 20 DFU. Depending on the results of the interim analysis a recommendation may be made to stop the study prematurely due to efficacy or futility.		
Statistical Rationale Provided:	✓	Yes	Refer to Section 11 for Sample Size Justification.
		No	

Variable(s):	PRIMARY:	Percentage change in target ulcer area, following treatment with either PICO or tNPWT, from baseline over the 12 treatment weeks.
	KEY SECONDARY:	Percentage change in target ulcer depth and volume, following treatment with either PICO or tNPWT, from baseline over the 12 treatment weeks.
	SECONDARY:	• Time (days) to confirmed complete target ulcer closure either through surgical intervention or by secondary intention, from baseline over the 12 treatment weeks. • Proportion of subjects that achieve confirmed complete target ulcer closure either through surgical intervention or by secondary intention from baseline over the 12 treatment weeks. • Difference in subject reported outcomes (response) from the Cardiff Wound Impact Schedule (CWIS) between initial assessment at Study Visit 1and at the End of Treatment period. • Difference in subject reported outcomes (response) from the EuroQol Group 5 Dimensions Questionnaire (EQ-5D) between initial assessment at Study Visit 1 and at the End of Treatment period.

EXPLORATORY:

Assessment of a difference in the following target ulcer assessments weekly over 12 weeks:

Condition of target ulcer peri-wound skin: Investigator response to a 7-category scale of the peri-wound skin condition.

Estimation of tissue types present on the target ulcer: Investigator response to a modified Bates-Jensen wound assessment tool.

Clinical signs and symptoms of infection on the target ulcer: Presence or absence of the clinical signs of infection (i.e., redness, swelling, tenderness, heat, purulence) as assessed by the Investigator or confirmed (i.e., microbiological culture) clinical infection, in the target ulcer.

Need for administration of antibiotics: Administration of antibiotics for a target ulcer infection.

Pain on removal of dressing: Subject response to the level of pain as recorded on the VAS during the removal of the NPWT dressing.

Pain on initiation of therapy/during dressing wear: Subject response to the level of pain as recorded on the VAS during the initiation of NPWT therapy (dressing draw-down) and during wear.

Dressing wear time: Time (days) between dressing changes.

Number and reason for dressing changes: Total number of dressing changes over the 12week treatment period and the documented reason for a dressing change.

Closure method: The number of subjects that undergo a surgical intervention (closure by simple flap, Split-Thickness Skin Graft (STSG), delayed primary intention with sutures).

Additional interventions: The number of subjects that require hospital admission, a surgical intervention for a wound related complication, or specialist referral for wound related complication.

Device trouble-shooting: The number and type of device trouble shooting episodes (alarm conditions/device failures/other malfunctions).

Impact of the device on aspects of daily living and satisfaction with device therapy: Subject response to a custom questionnaire to assess the impact of treatment with the device on subject's daily activities and satisfaction with the device.

SAFETY:	Recording of AE associated with the target ulcer and all SAE
PK:	NA

Adverse Device Effects:	✓	Both volunteered and elicited
		Other:

3. TABLE OF CONTENTS

3.1 TABLE OF TABLES

3.2 List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ABI	Ankle-brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BL	Baseline
BID	Twice Daily
BWAT-m	Bates-Jensen Wound Assessment Tool - modified
C/A	Causality Assessment
CBC	Complete Blood Count
CI	Confidence Interval
cm	Centimeters
cm^2	Centimeters squared or square centimeters (area)
cm^3	Centimeters cubed or cubic centimeters (volume)
CRF	Case Report Form
CMS	Centers for Medicare & Medicaid Services
CRO	Contract Research Organization
CV	Curriculum Vitae
D/C	Discontinued
DFU	Diabetic Foot Ulcer
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Glycated Hemoglobin
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
LCL	Lower Confidence Limit
LEU	Lower Extremity Ulcer

Abbreviation	Definition
LOCF	Last Observation Carried Forward
µg	Microgram
m^2	Meters squared or square meters (area)
mm	Millimeters
mmHg	Millimeters of mercury; a unit of pressure
mg/dL	Milligrams/deciliter
N or n	Sample Size
NA or N/A	Not Applicable
NIH	National Institutes of Health
NPWT	Negative Pressure Wound Therapy
NR	Not Related
NS	Not Sampled
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over-the-Counter
PAD	Peripheral Artery Disease
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
QD	Once Daily
QID	Four Times Daily
R	Related
RBC	Red Blood Cells
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAS	Statistical Analysis Software, SAS® Institute, Cary, NC
SD	Standard Deviation
SOC	Standard of Care
SOP	Standard Operating Procedures
STSG	Split-Thickness Skin Graft
TID	Three Times Daily
TM	Trademark
t NPWT	Traditional Negative Pressure Wound Therapy
Tx	Treatment
TX	Texas
UADE	Unanticipated Adverse Device Effect(s)
UCL	Upper Confidence Limit

Abbreviation	Definition
UPT	Urine Pregnancy Test
VAS	Visual Analog Scale
VLU	Venous Leg Ulcer
VSU	Venous Stasis Ulcer
WBC	White Blood Cells
WBP	Wound Bed Preparation

4. INTRODUCTION

4.1 BACKGROUND

Lower extremity ulcers are a chronic and debilitating condition caused by multiple disease processes that contribute to a high level of subject morbidity and healthcare spending in the United States[1]. The condition affects 1% of the adult population, and 3.6% of people older than 65 years, increasing to over 5% of people aged over 80 years[2]. Its prevalence in the community ranges from 1.9% to 13.1%, but this estimate is often under-reported as high numbers of subjects care for their ulcers at home, without consulting a healthcare provider[3]. It is thought that the incidence of ulceration is rising as a result of the aging population and increased risk factors for atherosclerotic occlusion such as smoking, obesity, and diabetes.

The common causes of lower leg ulceration are venous disease, arterial disease, and neuropathy. Less common causes are metabolic disorders, hematological disorders, and infective diseases. In venous disease, ulcers are usually located in the gaiter area between the ankle and the calf, often on the medial aspect of the leg. Venous ulcers arise from venous valve incompetence: valvular incompetence in the veins causes the vessels to become distended and stretch to accommodate the additional blood flow. The valves are not able to effectively close, which results in retrograde blood flow and venous hypertension. The venous hypertension, leads to leakage of fluid out of the stretched veins into the tissues, causing hemosiderin deposits in the gaiter area of the leg. Veins can be damaged by surgery, trauma, or Deep Vein Thrombosis (DVT), which causes a backflow of blood in the venous system at the point of damage. Other causative factors include multiple pregnancies, obesity, congenital vein abnormalities, varicose veins and calf muscle pump failure.

Diabetic foot wounds or ulcers are common and estimated to affect 15% of all diabetic individuals during their lifetime. For instance, an estimated 18% of diabetic patients over the age of 65 years in the US have non-healing foot ulcers[4,5,6]. It is now appreciated that 15–20% of patients with such foot ulcers go on to need an amputation. Almost 85% of the amputations are preceded by diabetic foot ulcers[7]. Worldwide, it is estimated that a lower limb is lost every 30 seconds as a result of diabetic wound infection.

Diabetic patients are at higher risk for arterial diseases and neuropathy and may develop ulcers due to both entities. Other factors in ulceration are trauma, deformity, callus formation, and edema.

Negative Pressure Wound Therapy (NPWT) is now widely used as the first line therapy in many wound management programs and there is growing evidence to support its clinical efficacy in the treatment of acute, traumatic and sub-acute wounds. NPWT is often used to regain control of a recalcitrant chronic wound; to kick start the healing process and progress the wound along a healing trajectory so that conventional wound therapy can be resumed with greater effect. NPWT is seldom used all the way through secondary intention closure, and often a surrogate marker of sufficient wound progression is used to signal that the wound is ready for a surgical intervention or for treatment with a lower acuity, (simple) advanced wound dressing.

Traditional Negative Pressure Wound Therapy (tNPWT) in its modern form has continued to evolve since its first inception in 1997 by Morykwas *et al.*,[8] and Argenta and Morykwas[9], but the basic principles of delivering sub-atmospheric pressure to the wound bed using a vacuum pump, connective tubing, a filler dressing and a polyurethane film to seal an open wound: making a closed wound (and system) have fundamentally remained the same. The use of NPWT has been widely reported across several indications and is considered an extremely effective therapy for the management of many different wound types compared to conventional treatment. While many different NPWT systems are now available, recently published comparative studies have demonstrated that clinical outcomes are largely equivalent[10,11,12]. Taken together, these studies show that NPWT is consistently effective across many wound types and care settings, irrespective of the simplicity or complexity of the source of the vacuum, type of wound filler or the level of pressure applied.

The NPWT evolution has really centered on the mechanical device delivering the negative (sub-atmospheric) pressure. Manufacturers have made vacuum pumps smaller, more light-weight and portable for patients and care-givers. PICO (Smith & Nephew Medical, Ltd) is a NPWT system which is an ultra-portable, canister-less system that can handle low to medium levels of exudate and is disposable (single-use) and battery operated.

4.2 PAST CLINICAL STUDIES

To assess whether PICO was able to operate effectively in a clinical environment, a "proof of concept" study was carried out in 20 patients, at two sites where PICO was used across a range of wound types. The mean dressing wear time was 4.6 days and 99% of patients found PICO comfortable in use. There were no device related complications (adverse events) during the study. Data chips placed inside the clinical study PICO devices proved that negative pressure was maintained very close to the set point of -80mmHg throughout the 7-10 days the devices were in place[13]. Reports from a similar independent study of 22 patients also show that PICO is flexible and readily deployed across many different wound types[14].

In a larger non-comparative North American evaluation, a total of 326 patients were treated with PICO in a community setting in Ontario, Canada[15]. The mean age of patients evaluated was 57 years old and 49.5% were male. The mean age of the wound was 8.9 weeks with a range from 1 week to 68 weeks and mean baseline wound area was 19.9cm^2. The wounds were a mix of surgical wounds (68%) that had become infected and split open (dehisced) and were delaying the patient's return to normal living, and chronic wounds; including both diabetic foot ulcers (5%) and venous leg ulcers (6%).

Wound type	Number of patients	Percentage of all wounds treated
Pressure ulcer	53	16%
Venous leg ulcer	21	6%
Diabetic foot ulcer	16	5%
Traumatic	15	5%
Surgical	221	68%

Wound types[15].

A total of 68% of wounds healed during the evaluation. Patients were, in general, pleased with the small discrete size of PICO that allowed them to continue normal daily activities.
In a further analysis of the study of 326 patients treated in a community setting in Ontario, the results from PICO patients were compared retrospectively with patients previously treated with traditional full-sized traditional NPWT[16]. Patients were matched on the basis of age, sex and wound characteristics. Patients with wounds greater than 100cm^2 and/or high levels of exudate

were excluded on the basis that these would be unsuitable candidates for treatment with PICO. The final cohort included in the analysis comprised 304 patients treated with PICO and 539 patients treated with NPWT. Wound area and volume were marginally greater in the NPWT arm although patients treated with PICO were older and had longer wound duration prior to treatment. The results showed that the reduction of wound area was very similar between PICO and traditional NPWT.

4.3 RATIONALE

Chronic wounds represent a significant burden to patients, healthcare providers and society as a whole. The economic burden of chronic wounds is often poorly understood or under-estimated. This occurs due to difficulties in capturing resource use and a failure to recognize wound management as a discipline. Generating improved outcomes and efficiency in the management of chronic wounds requires innovation[16].

NPWT addresses a number of different treatment objectives and allows consistent management of wounds across diverse clinical settings, and as a result, NPWT has become widely adopted as a treatment of choice in many clinical circumstances[17,18,19]. However, there have been some disadvantages. NPWT dressings and pumps can be complicated to apply and use. Even though NPWT can save nursing resources in the long run, providing the therapy can place a burden on healthcare budgets[20,21]. The need to be attached to a NPWT system with a bulky canister that collects the exudate can be intrusive for many patients[16]. The result is that NPWT tends to be reserved for only the most difficult wounds, whereas NPWT could be beneficial to a wider range of wounds especially in a community treatment setting.

The concept for PICO is to radically simplify the NPWT system to make it easier for the clinician to use. Wound dressings are pre-formed in a range of ready to use sizes and there is a single button to switch the device on at single most useful level of negative pressure. The system is easier for the patient to combine NPWT with life in their own home because the pump is small, lightweight and there is no need for an exudate canister. PICO is more cost effective on healthcare budgets by providing just the things that are necessary for effective NPWT and eliminating the things that are not. PICO is single-use and self-contained so there is no need for

the costs of administration for re-useable pumps or a separate supply of disposables. Each box contains two dressings and a single use pump. These design elements make PICO substantially less expensive than tNPWT systems. This allows PICO to be accessible to more patients who would benefit from NPWT but have previously been denied a chance of this therapy.

The aim of this study is to compare the clinical efficacy of two types of NPWT systems; 1.) tNPWT that has successfully completed a coding verification request with CMS and has the following capabilities (e.g., range of negative pressure, connective tubing, canister, foam or gauze filler, and approved for home use) and 2.) a portable, canister-less, battery operated, disposable single-use NPWT system (PICO) to see if there are any observed differences with regard to the clinical efficacy of the NPWT systems. The study will also assess if there are any additional health economic and health related quality of life (HRqOL) benefits to the patient and the care-giver in a community treatment setting that can be gained through the use of a small, battery operated, disposable single-use NPWT system.

A study that used a similar approach to that in the current protocol has previously been described[12,22,23]. In that investigation lower extremity ulcers compromising of diabetic foot and venous/mixed etiology ulcers were randomized to receive either electrically powered traditional NPWT devices (including ActiV.A.C.®) using a foam filler or a mechanically powered single-use NPWT device (SNaP) using a gauze filler. The study results showed that SNaP was non-inferior to ActiV.A.C.® using percentage area reduction as the primary endpoint. Quality of life and ease of use assessments also favored the single-use NPWT device over the traditional NPWT system.

5. OBJECTIVE(S)

PRIMARY

To compare PICO against tNPWT for the percentage change in the target ulcer area over the 12-week treatment period from baseline

KEY SECONDARY

To compare PICO against tNPWT for the percentage change in the target ulcer depth and volume over the 12-week treatment period from baseline

SECONDARY

1. To compare PICO against tNPWT in the time (days) to achieve confirmed complete target ulcer closure by either surgical intervention or secondary intention
2. To compare PICO against tNPWT for the proportion of subjects that achieve confirmed complete target ulcer closure by either surgical intervention or secondary intention
3. To compare PICO against tNPWT for differences in Health Related Quality of Life (HRQoL) over the 12-week treatment period

EXPLORATORY: Assessment of a difference in the following target ulcer assessments weekly over 12-week treatment period and to compare PICO against tNPWT:

- ☐ Condition of the target ulcer peri-wound skin
- ☐ Estimation of tissue types present on the target ulcer
- ☐ Clinical signs and symptoms of infection on the target ulcer
- ☐ Incidence of target ulcer infection
- ☐ Pain on removal of the dressing
- ☐ Pain on initiation of therapy/during dressing wear
- ☐ Dressing wear time
- ☐ Additional interventions
- ☐ Impact of the device on aspects of daily living and satisfaction with device therapy

SAFETY: Adverse events associated with the target ulcer area and all AE judged to be serious (SAE) will be recorded

6. TEST ARTICLE

6.1 IDENTIFICATION

Test Article: PICO - Single-Use Negative Pressure Wound Therapy (NPWT) System

Six (6) sizes of dressing are available in kits which contain 2 dressings, 1 pump and secondary fixation strips:

10cm x 20cm / 4in. x 8in. 66800951
10cm x 30cm / 4in. x 12in. 66800952
15cm x 15cm / 6in. x 6in. 66800954
15cm x 20cm / 6in. x 8in. 66800955
15cm x 30cm / 6in. x 11¾in. 66800956
20cm x 20cm / 8in. x 8in. 66800957

PICO Filler Dressings:

PICO foam and gauze filler dressing kits

Control Article: tNPWT devices that have successfully completed a coding verification request with CMS, are portable, FDA cleared, and have the following capabilities (e.g., range of negative pressure, connective tubing, canister, foam or gauze filler, and approved for home use) and have the indication to treat VLU and DFU.

6.2 USAGE

PICO:

The PICO Single Use Negative Pressure Wound Therapy System consists of a pump and two sterile dressing kits. The PICO pump maintains negative pressure wound therapy (NPWT) at -80 mmHg (nominal) +/- 20 mmHg to the wound surface. Exudate is managed by the dressing through a combination of absorption and evaporation of moisture through the outer film.

PICO is intended for use in wound sizes (surface area x depth) up to 400 cm^3, which are considered to be low to moderately exuding. The kit is intended to be used for a maximum of 7 days on low exuding wounds and 6 days on moderately exuding wounds. Therapy duration of the kit may be less than indicated if clinical practice or other factors such as wound type, wound

size, rate or volume of exudate, orientation of the dressing or environmental conditions, result in more frequent dressing changes. PICO may be used either with a filler (foam or gauze), placed into the wound where greater granulation stimulation is required, or without any foam or gauze wound filler.

tNPWT:

Please refer to Appendix 18.11 for the list of Sponsor-approved tNPWT devices.

6.3 PACKAGING AND LABELING

Packaging and labeling will be prepared to meet regulatory requirements. For any sites located outside the United States, the package labeling will be translated into the local language.

The packaging/labeling on the PICO test article kit contain the following information:

- Name of Sponsor
- Study Number
- Expiry Date
- LOT Number
- "MUST be Stored at Room Temperature"
- **Exclusively for Clinical Evaluation Only**

6.4 TEST ARTICLE ACCOUNTABILITY PROCEDURES

The sponsor company (Smith & Nephew, Inc.) will keep a detailed record of all investigational product, ancillary product and study supplies/materials supplied to each site. Confirmation of receipt of the investigational product/ancillary product and any other study materials/supplies, by the Investigator will also be retained.

Study Supply Request forms will be provided for any additional products/materials needed to complete the study.

The receipt and dispensing of the study treatment will be recorded on appropriate accountability forms available for verification by the Sponsor or its designated representative at each

monitoring visit. Used investigational devices must not be discarded or destroyed by site staff. All used devices will be retained at room temperature in their original packages until checked by the study monitor, after which they will be released to the site for destruction or will be returned back to the Sponsor.

All investigational products will be clearly identified as per the labelling in section 6.3.

The Study Monitor will ensure that the procedures and records are in place for the appropriate reconciliation of all investigational products. As part of monitoring, the Study Monitor will check that the site personnel are following the procedures and completing all the necessary documentation.

6.5 CONCOMITANT THERAPY

Subjects will be instructed about care of their target ulcer area over the duration of the study.

Subjects are not allowed to use any topical lotions or ointments applied directly to the target ulcer, beneath the PICO or tNPWT wound dressing kits, as this may interfere with the delivery of topical Negative Pressure Wound Therapy to the target wound, and the ability of the wound dressing kits to obtain a good seal in the peri-wound area.

Antibiotics (oral or systemic) will be allowed if a subject develops an infection requiring treatment after being randomized into the study.

No chemotherapy, immunotherapy, systemic hormonal therapy (other than hormone replacement therapy, hormonal contraceptives, and inhaled steroids), radiation therapy, or experimental medications will be permitted while subjects are in the study.

With the exceptions noted above, any medications that are considered necessary for the subject's welfare that will not interfere with the study treatment may be given at the discretion of the Investigator. This includes any standard care for non-target ulcers deemed appropriate by the Investigator and not prohibited by this protocol. Administration of all concomitant medications must be documented, along with dates of administration and reasons for use.

Simultaneous participation in other clinical trials evaluating experimental treatments or procedures is not permitted.

7. SUBJECTS

7.1 SUBJECT POPULATION

A total of approximately 160 subjects, presenting with a lower extremity ulcer (VLU or DFU) will be recruited at approximately 15 investigational centers in the United States and Canada, but potentially including investigational centers located in the United Kingdom and European Union. Additional sites may be added, if necessary to meet recruitment goals. As a restriction within the total of 160 subjects, a minimum of 46 subjects presenting with a DFU will be recruited along with minimum of 100 subjects presenting with a VLU will be recruited, the remainder of recruitment will comprise of subjects with either ulcer type.

An interim analysis will be performed after 80 subjects have completed the study, including a minimum of 40 VLU and 20 DFU, at which point a recommendation may be to stop the study prematurely due to either efficacy or futility. The stopping criteria are detailed in the Statistical Analysis Plan (SAP).

7.2 INCLUSION CRITERIA

1. Provide informed consent, which will consist of reading, signing, and dating the informed consent document after the Investigator, sub-Investigator or other designated study staff member has explained the study procedures, risks, and contact information.
2. Age $\geq$ 18 years, Male or Female.
3. Willing to comply with protocol instructions, including allowing all study assessments.

4. Women of child-bearing potential (those who are not premenarchal, not surgically sterilized [hysterectomy or bilateral oophorectomy], or not post-menopausal), may participate in the study if they meet all of following conditions:

    - Not breast feeding
    - A negative urine pregnancy test at screening
    - Agree to undertake a urine pregnancy test upon exiting the study
    - Do not intend to become pregnant during the study
    - Using adequate birth control methods and agree to continue using those methods for the duration of the study

    NOTE: Women who have had a bilateral tubal ligation are not considered to have been surgically sterilized and must agree to the conditions as specified above. Post-menopausal is defined as no menstrual period for at least one year.

5. Target ulcer involves a full thickness skin loss, but in the case of VLU, WITHOUT exposure of tendon, muscle, or bone.

6. Acceptable state of health and nutrition with pre-albumin levels of $\geq$ 10 mg/dL (0.10 g/L), serum albumin $\geq$ 2.0 g/dL (20 g/L), per the Screening central lab report, and no abnormal laboratory values that, in the opinion of the Principal Investigator, place the subject at risk for the trial.

7. An HbA_{1C} < 12.0% (108 mmol/mol) per the Screening central lab report.

8. Arterial supply adequacy confirmed by any one of the following:

    - Systolic blood pressure Ankle Brachial Index (ABI) in the range $\geq 0.70 \leq 1.20$
    - Great toe pressure $\geq$ 40 mm/Hg
    - $TcPO_2 \geq$ 30 mmHg from the foot
    - Normal triphasic or biphasic waveform pattern at the ankle
    - If ABI > 1.20 (**DFU subjects only**), perfusion at or near the site of the ulcer should be confirmed; the foot is warm to the touch and has palpable pulses.

9. **Subjects with a Venous Leg Ulcer (VLU):**

A. Should have an ulcer between the knee and ankle (at or above the malleolus), with a surface area ≥ 2.0 cm^2 and ≤ 36.0 cm^2 confirmed using the ARANZ Silhouette wound imaging and measurement device.

- If the subject presents with > 1, but ≤ 3 venous leg ulcers on the same leg, the largest qualifying ulcer will be selected as the target ulcer.
- A true single target ulcer MUST be at least 2.0 cm from any other VLU and will be used for treatment and evaluation throughout the trial.

B. Target ulcer duration ≥ 4 weeks but ≤ 104 weeks (24 months).

C. The subject is suitable for multi-layer compression therapy and is willing to tolerate the synergistic use of NPWT and multi-layer compression bandages.

D. Documentation that subject has failed previous therapy (e.g., compression therapy).

10. **Subjects with a Diabetic Foot Ulcer (DFU):**

A. Should have an ulcer present on any part of the plantar or dorsum surface of the foot, with a surface area ≥ 0.5 cm^2 and ≤ 10.0 cm^2 confirmed using the ARANZ Silhouette wound imaging and measurement device.

- Separation of at least 5.0 cm (closest ulcer edge to other closest ulcer edge) if $\geq$ 2 ulcers are present.

B. Target ulcer duration ≥ 4 weeks but ≤ 52 weeks (12 months).

C. Diabetes mellitus (Type 1 or 2) requiring insulin or oral/injectable medications to control blood glucose levels.

7.3 EXCLUSION CRITERIA

1. Subjects with known allergies to product components (silicone adhesives and polyurethane films (direct contact with wound), acrylic adhesives (direct contact with skin), polyethylene fabrics and super-absorbent powders (polyacrylates) (within the dressing) or any contraindications with the use of NPWT (see Appendix 18.1).
2. Therapy with another investigational agent within thirty (30) days of Screening (Run-in Visit 1), or during the study.
3. Ulcers which are deemed as highly exuding, per the Investigator's discretion.
4. Current diagnosis of osteomyelitis at the target wound location that is not currently receiving treatment [Documented history of resolved osteomyelitis is allowed].
5. Malignancy in the target ulcer, or history of cancer in the preceding 5 years (other than carcinoma in situ of the cervix or adequately treated non-melanoma skin cancers).
6. Clinical evidence of target ulcer bed infection.
7. Current diagnosis of vasculitis or current diagnosis of claudication.
8. Current systemic therapy with cytotoxic drugs.
9. Current therapy with chronic (> 10 days) oral corticosteroids.
10. Previous treatment with NPWT device or hyperbaric oxygen within 7 days of screening.
11. Per Screening central lab hematology report, WBC $< 2.0 \times 10^9$/L, neutrophils $< 1.0 \times 10^9$/L, platelets $< 100 \times 10^9$/L, and Hgb < 8.0 g/dL.
12. Per Screening central lab chemistry report, serum total bilirubin or serum creatinine ≥ 2 times the upper limit of the normal value (ULN); or, aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase ≥ 3 times ULN.
13. The ulcer is in a location that is non-amendable to the creation of an airtight seal for the effective delivery of topical NPWT to the ulcer surface.

14. **Subjects with a Venous Leg Ulcer (VLU):**
    A. A target ulcer of non-venous etiology (e.g., sickle cell anemia, necrobiosis lipoidica diabeticorum, pyoderma gangrenosum, vasculopathic or vasculitic).
    B. Deep Vein Thrombosis (DVT) that is acute, defined as the first 10 days from onset of symptoms, or any DVT for which compression bandaging is considered by the Investigator to be contraindicated.
    C. Refusal of or inability to tolerate compression therapy
15. **Subjects with a Diabetic Foot Ulcer (DFU):**
    A. Diagnosis of active Charcot foot syndrome
    B. Target wound location on toes

7.3.1 Additional Exclusion Criteria Prior to Randomization

Furthermore at the end of the run-in period, prior to randomization, the following exclusion criteria will apply for all subjects:

16. A reduction of the target ulcer area $\geq$ 30% during the Run-in period.
17. Use of excluded concomitant medications, therapies, or procedures during the Run-in period.
18. A clinically diagnosed infection of the target ulcer requiring treatment.
19. Muscle, tendon, or bone exposure in the target ulcer (**VLU Subjects only**).
20. Severe uncontrolled edema of the target ulcer leg (**VLU Subjects only**).
21. The subject is not able to tolerate compression therapy as required by the protocol (**VLU Subjects only**).
22. The target ulcer is > 15 cm in one linear direction, confirmed by the ARANZ Silhouette wound imaging and measurement device (**VLU Subjects only**)
23. In the judgment of the Investigator, the subject is not an appropriate trial subject.

7.4 SCREENING LOG

Participating study sites are required to document all screened subjects initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and noted on the Screening Log.

8. STUDY DESIGN

8.1 STUDY DESIGN

This is a multi-center, Phase 4, randomized, open-labelled, comparative-effectiveness study in subjects with at least one lower extremity wound (VLU or DFU). Approximately 160 subjects, including a minimum of 100 subjects presenting with VLU and 46 presenting with DFU, will be randomized to one of two treatment groups in an equal allocation to receive either PICO single-use NPWT system or tNPWT system, for 12 weeks, or until target ulcer closure (by surgical intervention or secondary intention), whichever occurs first.

Subject randomization to trial treatment will be conducted using an online randomization system and will be stratified by the subject's ulcer type and ulcer size (cm^2) at baseline. Each stratification factor will contain two levels: Venous Leg Ulcer or Diabetic Foot Ulcer, and Small or Large Ulcer with the definition of small and large dependent on ulcer type. The result will be four possible strata:

- Venous Leg Ulcer $\leq 12cm^2$ (small)
- Venous Leg Ulcer $> 12cm^2$ (large)
- Diabetic Foot Ulcer $\leq 2cm^2$ (small)
- Diabetic Foot Ulcer $> 2cm^2$ (large)

Further details regarding the randomization process will be provided in the SAP.

An interim analysis will be performed after 80 subjects have completed the study, incorporating a minimum of 40 VLU and 20 DFU.

8.2 METHODS USED TO MINIMIZE BIAS

The study is open-label due to visible differences in trial treatment devices. The use of random treatment allocation during the study will ensure that any selection bias (conscious or unconscious) on the part of the Investigator is avoided.

9. STUDY PROCEDURE

For a summary of the required procedures by visit, refer to Table 17-1: *Study Plan.*

9.1 VISITS AND EXAMINATIONS

9.1.1 Screening Run-in Visit 1

Assign a subject ID number to each subject who enters screening.

NOTE 1: Subjects who enter screening should have the potential heal, with excessive edema and infection under control.

NOTE 2: Any subject who signs an informed consent, but fails to meet the required entry criteria is considered to be a Screen Failure. Screen Failure subjects should have their demographic information captured with the reason for screen failure specified. Subjects may be re-screened 2 times. If a subject fails to meet all criteria after 3 screening attempts, the subject may not be enrolled into the study. A new informed consent is required for each screening attempt. All procedures, excluding the central lab, ABI, Toe Pressure, or $TcPO_2$ obtained within 30 days of re-screening, must be repeated for each screening attempt.

1. Explain the purpose and nature of the study, and have the subject or the subject's legally authorized representative **read**, **sign**, and **date** the IRB-approved informed consent document. Additionally, have the individual who obtains consent from the subject sign and date the informed consent document. Provide a photocopy of the signed informed consent document to the subject and place the original signed document in the subject's chart. Documentation of the informed consent process should be captured in each subject's source for each consenting.

----- Do not proceed until consent has been obtained -----

2. Screen the subject against the protocol inclusion and exclusion criteria for eligibility.
3. Obtain basic demographic information and relevant medical history, including information on all concomitant medications.
4. Complete a physical examination, body weight, height, and vital signs, including measurement of resting heart rate, respiratory rate, and blood pressure while seated.
5. Obtain complete history pertinent to the lower extremity target ulcer, including duration of the target ulcer, previous and current treatment and any other history that may have impacted the target ulcer (has it healed and re-occurred in the same location).
6. Assess target ulcer level of pain using the VAS.
7. Perform ulcer debridement if indicated. Debridement may only be performed using a curette, scissors, scalpel, or forceps.
8. Photograph and determine the post-debridement ulcer area (cm^2), perimeter (cm), greatest depth (mm), volume (cm^3) and maximum linear dimension (cm) using the ARANZ Silhouette wound imaging and measurement device.

   If debridement is not performed, an image of the target ulcer is still required to determine the ulcer area (cm^2), perimeter (cm), greatest depth (mm), volume (cm^3) and maximum linear dimension (cm) using the ARANZ Silhouette wound imaging and measurement device.

9. Assess arterial supply adequacy of target limb by way of ABI. If ABI is out of range (> 1.20) or is not able to be performed at the investigational center, then an alternative test can be used to confirm arterial supply adequacy (e.g., Great Toe Pressure, $TcPO_2$, or normal triphasic or biphasic waveform pattern at the ankle).

   Additional options for DFU subjects are available to confirm arterial supply adequacy:

   - If ABI > 1.20, perfusion at or near the site of the ulcer should be confirmed; the foot is warm to the touch and has palpable pulses.

10. Obtain blood samples for hematology, chemistry, serum pre-albumin and HbA_{1C} levels (send blood to central laboratory for analysis).

    All females of child-bearing potential (including those who have had a bilateral tubal ligation) will undergo a urine pregnancy test and the results will be analyzed and documented by the site personnel.

11. Apply Iodoflex or Iodosorb as antimicrobial dressing plus ALLEVYN and PROFORE multi-layer compression bandaging (**For VLU subjects**).

    Apply Iodoflex or Iodosorb as antimicrobial dressing and ALLEVYN Life (**For DFU subjects**).

12. If any adverse events in the target ulcer have occurred as a result of the screening or run-in procedures, the events must be reported and evaluated as instructed in Section 12, *Adverse Events*.

13. Subjects who do not meet eligibility will be screen failed and discharged, noting the reasons for disqualification.

14. Subjects who qualify to enter the run-in period will be instructed to refrain from using excluded medications and to return to the office for Screening Run-in Visit 2 within 7 (± 1) days.

9.1.2 Screening Run-in Visit 2 [7 (± 1) Days After Screening Run-in Visit 1]

At Screening Run-in Visit 2 the following procedures will be performed prior to randomization, to assure that none of the exclusion criteria described in Section 7.3.1 are met. The Screening Run-in Visit 2 should occur at 7 (± 1) days after Screening Run-in Visit 1. The day on which this visit occurs will set the weekly visit day for all subsequent treatment Visits 2 through 12 if the subject is randomized. A (± 1) day visit window will be allowed. Subjects who do not return on the original day of the week for a scheduled visit at Study Visits 2-12 should be brought back on the original scheduled day at the subsequent visit. Subjects who do not meet all eligibility criteria will be considered screen failures and documented as such. Subjects who meet all entry criteria will complete the randomization procedure and this visit will then serve as Study Visit 1.

1. Subjects will be queried regarding any changes in general health and the use of concomitant medications.
2. If any adverse events in the target wound have occurred as a result of the screening or run-in procedures, since the last assessment, the events must be reported and evaluated as instructed in Section 12, *Adverse Events*.
3. Remove compression bandaging (**for VLU subjects**) and topical dressing (**both VLU/DFU subjects**) to assess the target ulcer.

   Examine the ulcer for evidence of infection. If signs/symptoms indicate infection, remove the subject from the Run-in period as a screen failure.
4. Assess level of pain, post dressing removal, using the VAS.
5. Debride the ulcer if indicated, at the discretion of the Investigator.

   After debridement if presence of necrotic tissue or eschar within the target ulcer, subject should be screen failed.
6. Photograph and determine the post-debridement ulcer area (cm^2), perimeter (cm), greatest depth (mm), volume (cm^3) and maximum linear dimension (cm) using the ARANZ Silhouette wound imaging and measurement device. This is the baseline

ulcer assessment measurement.

If debridement is not performed, an image of the target ulcer is still required to determine the ulcer area (cm^2), perimeter (cm), greatest depth (mm), volume (cm^3) and maximum linear dimension (cm) using the ARANZ Silhouette wound imaging and measurement device. This is the baseline ulcer assessment measurement.

Calculate the percent change in ulcer area.

$$\Delta = \frac{Area_{RV2} - Area_{RV1}}{Area_{RV1}} \; x \; 100\%$$

If (Δ) percent change ≥ 30% decrease in target ulcer area; subject will be excluded from randomization and participation in the study.

9.1.3 Randomization Study Visit 1

This visit is a continuation of Screening Run-in Visit 2 for all eligible subjects and should be completed on the same day.

Upon completion of all Screening Run-in Visit 2 procedures and confirmation that the subject is eligible for the study, the Investigator or designee will register the subject using an electronic randomization system to calculate the percent change in the target ulcer. If the subject's percent change meets the eligibility criteria the subject will be randomized and then will enroll into the treatment period of the study. The randomization will be stratified based on target ulcer size and wound type observed at the screening visit. The details of the stratification factors and the process of the stratified randomization will be provided in the SAP. The subject will then receive the study treatment allocated to that subject identification number per instructions received from the electronic randomization system. Then the following procedures will be completed:

1. Subjects will be randomized using an electronic randomization system (www.sealedenvelope.com) to either treatment with PICO or tNPWT systems, and assigned a subject randomization number.
2. Conduct an ulcer assessment using the modified Bates-Jensen wound assessment

tool and record percentage tissue type/condition of peri-wound skin assessment (Normal, Erythematous, Edematous, Eczematous, Excoriated, Macerated, Indurated).

3. Ask the subject to complete the Cardiff Wound Impact Schedule (CWIS) quality of life questionnaire and EQ-5D.
4. Application of investigational product (PICO) or comparator tNPWT system according to randomization schedule.

   Record any additional dressings used and rationale for using this dressing.

   Type of wound filler dressing if used (foam or gauze-based filler dressing).

   Number of personnel used to apply NPWT system.

   Time used to apply NPWT system (minutes).

   Record level of negative pressure, intensity setting and delivery mode selected for tNPWT subjects, if appropriate for device selected.

   Apply Profore compression bandage over the NPWT dressing for VLU subjects only.
5. Record subject's level of pain, during initiation of NPWT therapy, using VAS.
6. Subjects will be instructed to refrain from using excluded medications, and to return to the office for Study Visit 2 in 7 (± 1) days.

   Subjects using a negative pressure filler dressing will be instructed to complete a dressing change in 2-3 days from application.

9.1.4 Study Visits 2-12

The treatment period is defined as Randomization Study Visit 1 through Study Visit 12. During the study treatment period, any AE associated with the target ulcer and all SAE of any kind will be recorded in the appropriate eCRF. Device deficiencies (DevD) will be recorded in a separate eCRF. The evaluation of all AE is described in Section 12, *Adverse Events*. All weekly visits

must be performed according to the study visit schedule (Section 17), preferably on the same day each week, to conduct all assessments and to assure compliance with treatment. A plus or minus one day visit window will be used for all study visits.

VLU subjects found to have target ulcer closure should continue the compression dressing. Appropriate treatment for DFU subjects found to have target ulcer closure is left to the Investigator's discretion. Appropriate treatment for VLU and DFU subjects, whose target ulcer is ready for and will be surgically closed, is left to the Investigator's discretion. If the Investigator believes the target ulcer is ready for surgical closure, then this procedure should be completed within the same week of the scheduled study visit. The next scheduled visit for subjects with closed target ulcers or subjects that will be surgically closed will be designated as End of Treatment Assessment Visit 14 and should occur in 7 (±1) days.

All study procedures should occur in the order outlined in the protocol. Study Visits occurring outside the protocol specified visit window should be completed and recorded as a protocol deviation.

1. Subjects will be queried regarding any changes in general health and the use of concomitant medications.
2. Any AE associated with the target ulcer and all SAE of any kind reported since the last assessment will be recorded in the appropriate eCRF. DevD will be recorded in a separate eCRF (see "Section 12, *Adverse Events"* for reporting and evaluating AE). Also, subjects will be queried as to any additional ulcer-related interventions requiring hospital admission, surgical intervention or specialist referral since the last assessment.
3. Assess level of pain from NPWT dressing wear, since the previous study visit, using the VAS.
4. Prior to examination of the ulcer, remove compression bandaging (**for VLU subjects)** and photograph the NPWT topical dressing using the ARANZ Silhouette wound imaging and measurement device.

5. Remove NPWT topical dressing to assess the target ulcer.
6. Assess level of pain, post NPWT dressing removal, using the VAS.
7. Complete reason for dressing change assessment and record any additional dressing changes since previous assessment as an unscheduled visit.
8. Assess target ulcer and record if target ulcer is closed or if target ulcer is ready for and will be surgically closed.

   Note 1: If the target ulcer is closed, skip procedures 9-15 and complete procedure 16.

   Note 2: If target ulcer is ready for and will be surgically closed, skip procedures 9-16 and complete procedure 17.
9. Examine the ulcer for evidence of infection, and treat the infection as appropriate per local protocol.
10. Debride the ulcer if indicated, at the discretion of the Investigator.
11. If the target ulcer remains open, photograph and determine the post-debridement ulcer area (cm^2), perimeter (cm), greatest depth (mm), volume (cm^3), and maximum linear dimension (cm) using the ARANZ Silhouette wound imaging and measurement device if applicable.

    If debridement is not performed, an image of the target ulcer is still required to determine the ulcer area (cm^2), perimeter (cm), greatest depth (mm), volume (cm^3) and maximum linear dimension (cm) using the ARANZ Silhouette wound imaging and measurement device.
12. Conduct an ulcer assessment using the modified Bates-Jensen wound assessment tool and record percentage tissue type/condition of peri-wound skin assessment (Normal, Erythematous, Edematous, Eczematous, Excoriated, Macerated, Indurated).
13. Re-application of investigational product (PICO) or comparator tNPWT system

according to randomization schedule.

Record any additional dressings used and rationale for using this dressing.

Type of wound filler dressing if used (foam or gauze-based filler dressing).

Number of personnel used to apply NPWT system.

Time used to apply NPWT system (minutes).

Record level of negative pressure, intensity setting and delivery mode selected for tNPWT subjects, if appropriate for device selected.

Apply Profore compression bandage over the NPWT dressing for VLU subjects only.

14. Record subject's level of pain, during initiation of NPWT therapy, using VAS.
15. Subjects will be instructed to refrain from using excluded medications, and to return to the office for their next study visit in 7 (± 1) days.

    Subjects using a negative pressure filler dressing will be instructed to complete a dressing change in 2-3 days from application.
16. **For subject's whose target ulcer has closed during the treatment period, the following procedures should be completed**:

    - Photograph and signify the ulcer as closed using the ARANZ Silhouette wound imaging and measurement device.
    - Subjects to complete Cardiff Wound Impact Schedule (CWIS) quality of life questionnaire and EQ-5D.
    - Apply only Profore compression bandage for VLU subjects
    - Appropriate treatment for DFU subjects is left to the Investigator's discretion
    - Subjects will be instructed to refrain from using excluded medications and to return to the office for End of Treatment Assessment Visit 14 in 7 (± 1)

days.

17. **For subject's whose target ulcer will be surgically closed, the following procedures should be completed**:

- Photograph and determine the ulcer area (cm^2), perimeter (cm), greatest depth (mm) and volume (cm^3) using the ARANZ Silhouette wound imaging and measurement device.
- Conduct an ulcer assessment using the modified Bates-Jensen wound assessment tool and record percentage tissue type/condition of peri-wound skin assessment (Normal, Erythematous, Edematous, Eczematous, Excoriated, Macerated, Indurated).
- Subjects to complete Cardiff Wound Impact Schedule (CWIS) quality of life questionnaire and EQ-5D.
- Appropriate treatment for VLU and DFU subjects is left to the Investigator's discretion
- Subjects will be instructed to refrain from using excluded medications and to return to the office for End of Treatment Assessment Visit 14 in 7 (± 1) days.

9.1.5 Study Visit 13

If a subject's ulcer is judged to have not closed at Visit 13, this will be noted and the subject will not complete the procedures for this Visit, but will complete the End of Treatment Assessment or Early Discontinuation Visit 14 procedures noted in Section 9.1.6.

However, if the target ulcer is observed to be closed at Visit 13 or will be surgically closed at this visit, the following procedures will be completed at this visit and the subjects will be instructed to return to the office in 7 (± 1) days for End of Treatment Assessment Visit 14. If the Investigator believes the target ulcer is ready for surgical closure, then this procedure should be completed within the same week of the scheduled study visit.

1. Subjects will be queried regarding any changes in general health and the use of concomitant medications.
2. Any AE associated with the target ulcer and all SAE of any kind reported since the last assessment will be recorded in the appropriate eCRF. DevD will be recorded in a separate eCRF (see "Section 12, *Adverse Events"* for reporting and evaluating AE). Also, subjects will be queried as to any additional ulcer-related interventions requiring hospital admission, surgical intervention or specialist referral since the last assessment.
3. Assess level of pain from NPWT dressing wear, since the previous study visit, using the VAS.
4. Prior to examination of the ulcer, remove compression bandaging (**for VLU subjects**) and photograph the NPWT topical dressing using the ARANZ Silhouette wound imaging and measurement device.
5. Remove NPWT topical dressing to assess the target ulcer.
6. Assess level of pain, post NPWT dressing removal, using the VAS.
7. Record any additional dressing changes since previous assessment as an unscheduled visit.
8. Assess target ulcer and record if target ulcer is closed or if target ulcer is ready for and will be surgically closed.
9. Photograph and signify the target ulcer as closed using the ARANZ Silhouette wound imaging and measurement device.

   If the target ulcer will be surgically closed, photograph and determine the ulcer area (cm^2), perimeter (cm), greatest depth (mm) and volume (cm^3) using the ARANZ Silhouette wound imaging and measurement device if applicable.

10. **Target ulcers open and ready for surgical closure only**:
    - Conduct an ulcer assessment using the modified Bates-Jensen wound assessment tool and record percentage tissue type/condition of peri-wound skin assessment (Normal, Erythematous, Edematous, Eczematous, Excoriated, Macerated, Indurated).
11. Apply only the Profore compression bandage for VLU subjects whose target ulcer is closed.

    Appropriate treatment for VLU subjects whose target ulcer will be surgically closed is left to the Investigator's discretion.

    Appropriate treatment for DFU subjects is left to the Investigator's discretion.
12. Subjects to complete Cardiff Wound Impact Schedule (CWIS) quality of life questionnaire and EQ-5D.
13. Subjects will be instructed to refrain from using excluded medications and to return to the office for End of Treatment Assessment Visit 14 in 7 (± 1) days.

9.1.6 End of Treatment Assessment or Early Discontinuation Visit 14

1. Subjects will be queried regarding any changes in general health and the use of concomitant medications.
2. Any AE associated with the target ulcer and all SAE of any kind reported since the last assessment will be recorded in the appropriate eCRF. DevD will be recorded in a separate eCRF (see "Section 12, *Adverse Events*" for reporting and evaluating AE). Also, subjects will be queried as to any additional ulcer-related interventions requiring hospital admission, surgical intervention or specialist referral since the last assessment.

3. **For subjects whose target ulcer remained open during the treatment period, the following procedures should be completed:**

    - Assess level of pain from dressing wear, since the previous study visit, using the VAS.
    - Prior to examination of the ulcer, remove compression bandaging (**for VLU subjects**) and photograph the NPWT topical dressing using the ARANZ Silhouette wound imaging and measurement device.
    - Remove NPWT topical dressing to assess the target ulcer.
    - Assess level of pain, post NPWT dressing removal, using the VAS.
    - Subjects to complete Cardiff Wound Impact Schedule (CWIS) quality of life questionnaire and EQ-5D

4. Record any additional dressing changes since previous assessment as an unscheduled visit.
5. Photograph and determine ulcer area (cm^2), perimeter (cm), greatest depth (mm) and volume (cm^3) for target ulcers that remain open or, if the target ulcer is closed or remained closed, photograph using the ARANZ Silhouette wound imaging and measurement device.
6. **For subjects whose target ulcer remained open during the treatment period or re-opened after initialing closing during the treatment period:**

    - Conduct an ulcer assessment using the modified Bates-Jensen wound assessment tool and record percentage tissue type/condition of peri-wound skin assessment (Normal, Erythematous, Edematous, Eczematous, Excoriated, Macerated, Indurated).

7. All females of child-bearing potential (including those who have had a bilateral tubal ligation) will undergo an exit urine pregnancy test upon completion or discontinuation from the study and the results will be analyzed and documented by the site personnel.
8. Document what next treatment is planned by the PI post-study for each target ulcer, regardless if open or closed.
9. Subject to complete satisfaction questionnaire
10. The subject will be exited from the study.

9.1.7 Unscheduled Visits

Unscheduled exams may be conducted at the discretion of the Investigator with all obtained information recorded in the source documents and on the Unscheduled Visit pages within the Case Report Form (CRF) booklet.

Subjects using a negative pressure filler dressing or using tNPWT will be instructed to complete a dressing change in 2-3 days from application. This visit should be captured as an unscheduled visit.

9.1.8 Concomitant Medications

A concomitant medication is any drug or substance administered from Screening Run-in Visit 1 of the study through the last study visit.

Since the ulcer treatments in this study are devices and treat only the target ulcer area covered by the device dressings, with no systemic effects, the only concomitant medications to be reported during this study in the eCRF are as follows:

- All current and past target ulcer treatments only (no doses will be recorded)
- Concomitant medications (no doses to be recorded) used to treat the target ulcer (e.g., systemic antibiotics for a target ulcer infection) and the peri-wound area (such as treatment for erythema, irritation, itching), together with the indication for the medication

- Concomitant medications used to treat all ADE, SADE, and UADE will be recorded in the appropriate eCRF forms

The use of all concomitant therapies must be recorded in the subject's source, together with any associated AE, SAE, ADE, ASADE or UADE, but only reported in the subject's eCRF as described above.

The following concomitant medications are not permitted during the study period:

- Systemic corticosteroids with daily administration of greater than 10 days
- Systemic drugs intended to function as immunosupressants
- Any target ulcer treatment, excluding study treatment or surgical procedures, specifically intended to close the ulcer
- Topical antibiotics to the target ulcer or to the target peri-wound area
- Mid- to superpotent topical steroids used for > 10 days
- Enzymatic debriders to target ulcer
- Systemic chemotherapy
- Radiation therapy directed to the affected limb
- Current or prior normothermic (Warm-UP®) or HBO therapy within 7 days of the Screening Run-in Visit 1, unless the tissue area has been fully excised

9.2 DISCONTINUED SUBJECTS

Discontinued subjects are those who voluntarily discontinue participation, who are withdrawn for safety reasons or who have missed a sufficient number of study visits, procedures or test article doses, as defined below, to be ineligible for further participation.

All subjects who discontinue the study prior to completing the regularly scheduled visits should complete the End of Treatment Assessment or Early Discontinuation Visit 14.

Any changes in medical health and/or the use of concomitant medications will be captured. If any SAE, target ulcer AE, or DevD were observed since the previous visit, they must be recorded (refer to Section 12, *Adverse Events*, for instructions on reporting and evaluation

procedures). All females of child-bearing potential must also undergo a urine pregnancy test upon exiting the study. Finally, if appropriate, the Investigator will also advise the subject of subsequent therapy and/or procedures necessary for their medical condition.

During the course of the study, the subject must be discontinued from study treatment in the case of any of the following:

- An infection of the target ulcer occurs and does not respond as expected to appropriate conventional treatment after 2 weeks of therapy
- Progressive disease defined by an increase of ≥ 75% in the ulcer surface area at any time during the treatment phase using the measurement from Run-in Visit 2 as the baseline target ulcer measurement. The increase is calculated as follows:

$$\left[\left(\frac{Area_{Vn} - Area_{RV2}}{Area_{RV2}}\right)\times 100\right] \geq 75$$

- Persistence of an SAE, device –related AE or abnormal laboratory value that in the opinion of the Investigator places the subject at risk should they continue in the study
- Subject misses > 2 weekly study visits during the treatment period.
- Subject misses 14 consecutive days of therapy or standard care treatment during the treatment period
- Subject misses 21 cumulative days of therapy during the treatment period

Subjects may be discontinued from the study at any time if, in the opinion of the Investigator, their continued participation in the study poses a risk to the subject. Additionally, subjects may be discontinued from the study for the following reasons:

- Adverse device effects
- Lost to follow-up
- Subject decision unrelated to an adverse device effects
- Noncompliance (e.g., did not follow instructions, took disallowed medications)
- Other

9.2.1 Replacement Policy

Subjects who dropout before being randomized (i.e., during the Screening or Run-in period) will be replaced. Subjects who drop out of the study after randomization, for whatever reason, will not be replaced.

Any subject who drops out after randomization will not be permitted to re-enroll into the study at a later date.

9.3 SUBJECT PREGNANCY

Women of child-bearing potential are not excluded from the study as long as adequate birth control methods are being utilized by the subject. However, if a woman becomes pregnant during the study, Smith & Nephew Inc. must be contacted immediately and a decision will be made regarding the continuation in the study of the pregnant woman. Pregnancy is not reportable as an adverse device effect; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis. Pregnancy-related information will be collected until termination of the pregnancy.

9.4 STUDY METHODS AND MEASUREMENTS

For purposes of derivation of endpoints and subsequent analysis, study treatment refers to either PICO or tNPWT. Four individual negative pressure wound therapy devices are available for use during the study; the data for the study endpoints collected for each of these individual devices will be pooled to constitute the tNPWT treatment arm.

Primary Endpoint

The primary endpoint for this study is the percentage change in target ulcer area over the 12-week treatment period. Target ulcer area is defined as surface area as measured by the ARANZ Silhouette Device (18.2) at each study visit by the Investigator. The percentage change in target ulcer area over the 12-week treatment period is then defined as:

$$\text{Percentage change in target ulcer area} = \left(\left(\frac{Area_{SV13} - Area_{SV1}}{Area_{SV1}}\right) \times 100\right)$$

In cases where the target ulcer area is closed in the opinion of the Investigator (regardless of 1-week confirmation), the ulcer area will be imputed as 0 cm^2, resulting in a percentage change in target ulcer area of 100%. In circumstances where the ulcer area is missing at the Study Visit 13 for subjects that have not withdrawn prematurely due to closure, the last observation carried forward (LOCF) method will be used.

Key Secondary Endpoints

The key secondary endpoints are the percentage change in the target ulcer dimensions not assessed as part of the primary endpoint, namely depth and volume. As defined for the primary endpoint, ulcer depth and volume will be measured by the ARANZ Silhouette Device at each visit by the Investigator, and the percentage change in depth and volume over the 12-week treatment period will then be defined as per the formula above replacing the area measurements with the corresponding depth and volume respectively.

Secondary Endpoints

The secondary endpoints are as follows:

- The proportion of subjects with confirmed ulcer closure (achieved by surgical intervention or secondary intention) during the 12-week treatment period. The subject's ulcer closure status (open or closed) will be assessed by the Investigator at each study visit. For purposes of analysis, a closed ulcer is defined as having complete re-epithelialization, without drainage or the need for a dressing; a confirmed closed ulcer is as a closed ulcer with closure status confirmed at a visit 1-week post initial closure. The derivation is as follows:
    - Ulcer Closed=Yes at last attended Study Visit i, Ulcer Closed=Yes at Follow up assessment (visit i+1)

- Confirmed Closure = Yes

- Ulcer Closed= Yes at last attended Study Visit i, Ulcer Closed=No at Follow up assessment (visit i+1)
  - Confirmed Closure = No

- Ulcer Closed=Yes at last attended Study Visit i, Ulcer Closed=missing at Follow up assessment (visit i+1)
  - Confirmed Closure = missing

- Ulcer Closed=No at last attended Study Visit i,
  - Confirmed Closure = No

In cases where the ulcer closure status is missing at a Study Visit, the Last Observation Carried Forward (LOCF) method will be used.

- The time in days to (confirmed) ulcer closure dressing during the 12-week treatment period (with confirmed closure as defined in the previous paragraph). Once a subject has achieved confirmed ulcer closure, either by surgical intervention or secondary intention, the time to healing will be calculated from the date of the randomization visit to the date at which the subject's ulcer was first recorded as closed:

  $$(\textit{Date of first Ulcer Closure visit} - \textit{Date of Randomization } (SV1))$$

  For those subjects that withdraw or do not achieve confirmed ulcer closure during the study, the time to complete ulcer closure will be censored at the last visit date attended. The resulting time to complete ulcer closure will be defined as:

  $$(\textit{Date of Last Study Visit attended} - \textit{Date of Randomization } (SV1))$$

Where the censored time to confirmed ulcer closure is greater than 84 days, this will be truncated to 84 days.

- The difference between treatments in the change in subject reported Quality of Life (QoL) during the 12-week treatment period. The Health related Quality of Life (HRQoL) will be assessed using the EQ-5D and CWIS validated instruments. Study subjects will complete both instruments at the Randomization Study Visit 1 and at the End of Treatment period. The change in continuous measures of the EQ-5D and CWIS instruments (including Time Trade-off (TTO) index, EQ-VAS, and domain averages) between the randomization Study Visit 1 and End of Treatment period will be derived as follows using the relevant variable:

  $$(Value\ at\ End\ of\ Treatment\ period - Value\ at\ Randomization\ Study\ Visit\ 1)$$

Exploratory Endpoints

The exploratory endpoints are as follows:

- Assessment of change in target ulcer progression parameters over the 12-weeks and comparison between treatments including: Estimation of the types of tissue present on the target ulcer, Presence of Infection/Clinical signs of infection, Condition of peri-wound skin, Need for administration of antibiotics and additional interventions, dressing wear time, pain on removal of dressing and at initiation of, and during, therapy.

  The subject's target ulcer will be assessed by the Investigator at each study visit. Where possible this assessment will be made using a modified Bates-Jensen wound assessment tool, this will include information concerning presence of Undermining, Necrotic Tissue Type and Amount, Exudate Type and Amount, Granulation Tissue and Epithelialization. Otherwise the Investigator's assessment against a custom descriptive scale will be used.

Condition of peri-wound skin will be assessed by the Investigator against a custom 7-category descriptive scale: Normal, Erythematous, Edematous, Eczematous, Excoriated, Macerated and Indurated. Presence of each skin type will be recorded.

Assessment of the presence of infection and clinical signs of infection will be undertaken by the Investigator.

Presence of Undermining, Necrotic Tissue Type and Amount, Exudate Type and Amount, Granulation Tissue and Epithelialization will be assessed using the modified Bates Jensen wound assessment tool.

Pain associated with removal of dressing, and at initiation of, and during, therapy will be assessed using the Pain VAS scale.

The need for administration of antibiotics and additional interventions in the opinion of the Investigator will be recorded.

The duration of dressing wear (dressing wear time) will be calculated using the visit date captured on the CRF and, if applicable, the date of additional/unscheduled dressing changes; by subtracting the date of dressing application from the date of dressing removal. The average wear time will then be derived for each subject using the following formulae. Average subject wear time = sum of duration of wear for the subject / number of dressings used by the subject.

9.5 HEALTH ECONOMICS/QUALITY OF LIFE

The impact of, and comparison of, trial treatments on subject Quality of Life is included as a secondary study objective. Namely, the difference between treatments in the change in subject reported Quality of Life (QoL) during the 12-week treatment period.

The Health Related Quality of Life (HRQoL) will be assessed using the EQ-5D and CWIS validated instruments. Study subjects will complete both instruments at the Randomization Study Visit 1 and at the End of Treatment period.

Resource use will also be captured and detailed by treatment, including the following: material usage (number of dressing applied and additional materials used), personnel usage (number of personnel, and time, required for dressing change), additional interventions and hospital admissions. Should quantifiable statistical differences be observed in any of the exploratory or safety assessments, a post-hoc health economic analysis will be conducted. This post-hoc analysis will examine the economic implications of the observed differences in resource utilization between the PICO and tNPWT groups by applying existing market prices to the resources utilized and comparing total direct costs between the two groups.

Resource use, as detailed in the previous paragraph, will also separately be detailed by individual tNPWT device.

10. STATISTICAL DESIGN

A formal Statistical Analysis Plan (SAP) (also referenced to as the Statistical Considerations) will be written and finalized prior to the trial commencing subject recruitment. The SAP will detail the summaries and analyses to be performed.

Smith & Nephew Wound Management Global Medical and Clinical Affairs Department will conduct data management and statistical analysis. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting P-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. All analyses will be performed in SAS v9.4 (or later).

Where data summaries are specified, categorical and ordinal variables will be summarized using frequency distributions which will detail the number and percentage of subjects which fall into each category. Continuous variables will be summarized using the following summary statistics: mean, median, standard deviation, minimum and maximum values, and number of observations.

For purposes of analysis, unless otherwise stated, treatment refers to either PICO or tNPWT. All data for individual negative pressure wound therapy devices used during the study will be pooled to constitute the tNPWT treatment arm. Where specified, additional summaries and analysis will be performed on individual tNPWT devices in addition to the overall tNPWT treatment arm.

10.1 EVALUABILITY

All subjects that are randomized at Study Visit 1 (baseline visit) are considered study participants. The following study populations and analysis sets will be defined:

Safety Population: This will include all subjects that are randomized to, and receive, one of the trial treatments.

Full Analysis Set: Using the Intent-to-treat (ITT) principle, this will include all subjects that are randomized and receive trial treatment, and attend at least one follow-up post baseline. Subjects will be analyzed according to treatment randomization.

Per Protocol Population (PP): This will include all subjects that are randomized to trial treatment, meet the inclusion/exclusion criteria, do not discontinue trial treatment within the first nine (9) weeks (- 1 day) and have no significant protocol deviations including the use of an unapproved tNPWT device as defined in the protocol. Subjects that achieve closure will be included regardless of time on therapy unless they are deemed to have significant protocol deviations or failed to meet the inclusion/exclusion criteria.

Statistical analysis will be performed using each of the subject populations as follows. Analysis of the primary, secondary and exploratory efficacy objectives will be performed separately using both the Full Analysis Set and the Per Protocol Population. All safety analyses will utilize the Safety Population.

10.2 HANDLING OF MISSING AND INCOMPLETE DATA

The methods used to handle missing or incomplete data for the efficacy and safety measures is be detailed in the SAP.

10.3 EFFICACY ANALYSIS

10.3.1 Primary Efficacy

The primary endpoint of the study is the percentage change in target ulcer area over the 12-week treatment period and will be analyzed as follows. An initial linear regression model will contain covariates for treatment, center, wound type, baseline (defined as Study Visit 1) target ulcer area and duration of target ulcer. For purposes of the primary analysis, any centers with less than 10 subjects will be pooled. A forward selection procedure will be used for the addition of other baseline covariates with an F-value to attain a significance level of 0.1. Further baseline covariates to be assessed as part of this procedure include: subject age, body mass index, baseline ulcer depth, ABI and baseline level of exudate. The resulting primary analysis presented will correspond to the final model from the forward selection procedure. The results for the initial model will also be presented. For each of the effects in the initial and final model, the p-value, parameter estimate and corresponding 95.4% confidence interval will be presented. Secondary subgroup analyses may be conducted as a result of the covariate analyses. Additionally, treatment will be fitted on its own in a further linear regression model. The potential for interactions, particularly treatment by center interactions will be examined by fitting the required interaction terms in addition to those effects in the final linear regression model from the forward selection procedure.

Non-inferiority will be concluded in each case if the upper bound of the 95.4% confidence interval for the parameter estimate relating to treatment covariate (coded as tNPWT – PICO) is less than (<) 12.5 which relates to the desired one-sided test at the 2.5% significance level after adjusting for the interim analysis.

If distributional and model assumptions relating to the above analysis do not hold, a permutation test will be used as a distribution free non-inferiority analysis. The sampling distribution of the test statistic will be estimated by re-randomization of treatments to each of the study subjects. At a minimum the completed re-randomization process will be repeated 2000 times. However, if 2000 replicates are found to be insufficient for the random variation in results of successive repeats to be reduced to an acceptable level, the number of replicates will be increased until such a point as consistent results are observed between successive repeats of the permutation tests.

Detailed stopping criteria can be found in the SAP. For purposes of the permutation analysis, to test against the null one-sided hypothesis of a difference greater than delta, the non-inferiority margin (delta=12.5%) will be added to, or subtracted from, the observed change in individual area measurement for those subjects that are re-randomized by the permutation test to the treatment which they were not randomized to during the trial. The resulting p-value will be derived as per usual bootstrapping techniques.

The primary analysis (detailed in the previous paragraphs) will be performed using the Per Protocol Population; the analysis will also be repeated using the Full Analysis Set. Differences in conclusions between the two analyses will be investigated. The ability to switch between non-inferiority and superiority will be considered only if both subject populations demonstrate non-inferiority.

Further details, including model assumptions and diagnostics to be examined are included in the study SAP.

The percentage change in ulcer area will be summarized by treatment and center (and overall). Further summaries will be produced separated by the covariates used in the final model.

10.3.2 Secondary Efficacy

The secondary efficacy variables include the percentage change in target ulcer depth and volume over the 12-week treatment period (the key secondary endpoints), the time (in days) to achieve complete target ulcer closure either by surgical intervention or secondary intention, the proportion of subjects that achieve complete target ulcer closure by surgical intervention or secondary intention, and the change in subject reported Quality of Life (QoL).

Percentage change in target ulcer depth and volume over the 12-week treatment period (Key Secondary)

The primary analysis and accompanying summaries relating to change in target ulcer area will be repeated separately for both the change in target ulcer depth and volume over the 12-week treatment period with a single exception. The initial models will include baseline ulcer depth and

volume respectively for the two key secondary objectives rather than baseline ulcer area as described in the primary analysis.

Proportion of subjects achieving confirmed target ulcer closure over the 12-week treatment period

The proportion of subjects achieving confirmed target ulcer closure, either by surgical intervention or secondary intention, over the 12-week treatment period will be analyzed as follows using the Full Analysis Set. An initial logistic regression model will contain covariates for treatment, center, wound type, baseline (defined as Study Visit 1) ulcer area and duration of ulcer. Pooling of centers with less than 10 subjects will be performed as described in the primary analysis. A forward selection procedure will be used for the addition of other baseline covariates with an F-value to attain a significance level of 0.1. Further baseline covariates to be assessed as part of this procedure include: subject age, body mass index, baseline ulcer depth, ABI and baseline level of exudate.

The resulting analysis presented will correspond to the final model from the forward selection procedure. The results for the initial model will also be presented. For each of the effects in the initial and final model, the p-value, odds-ratio and corresponding 95% confidence interval will be presented. Secondary subgroup analyses may be conducted as a result of the covariate analyses. Additionally, treatment will be fitted on its own in a further logistic regression model. In each case, the residuals will be examined for outliers using influence plots of diagnostic statistics; further details are included in the SAP.

Cross-tabulations of each of the covariates (continuous covariates will be categorized for purposes of the cross-tabulations) with treatment and closure, will be generated for each of the baseline covariates included in the final model.

The 95% confidence interval (unadjusted for all covariates) for the difference between treatments in percentage healed by 12 weeks will be generated along with the Chi-square test p-value using the Per Protocol Population.

Two separate sensitivity analyses will be performed to ensure that the efficacy findings are not reliant on assumptions made in either the analysis or derivations; the analysis for the proportion

of subjects achieving confirmed ulcer closure will be repeated with the following modifications using the Full Analysis Set only:

1) In cases where subjects had missing data over the confirmatory target ulcer closure period (1 week follow-up) and it is unknown whether the closure is confirmed, these will be imputed as: Confirmed Closure=No.

2) In cases where subjects withdraw from the study prior to the end of the 12-week treatment period (except in cases where the ulcer has closed), the following will be imputed: Confirmed Closure=Yes.

Time (days) to achieve confirmed target ulcer closure by surgical intervention or secondary intervention

A proportional hazards survival analysis will be applied to the time to achieve (confirmed) target ulcer closure using the Full Analysis Set. An initial proportional hazards model will include the covariates for treatment, center, wound type, baseline (defined as Study Visit 1) ulcer area and duration of ulcer. Pooling of centers with less than 10 subjects will be performed as described in the primary analysis. A forward selection procedure will be used for the addition of other baseline covariates with an F-value to attain a significance level of 0.1. Further baseline covariates to be assessed as part of this procedure include: subject age, body mass index, baseline ulcer depth, ABI and baseline level of exudate. The resulting analysis presented will correspond to the final model from the forward selection procedure. The results for the initial model will also be presented. For each of the effects in the initial and final model, the p-value, hazard-ratio and corresponding 95% confidence interval will be presented. Secondary subgroup analyses may be conducted as a result of the covariate analyses. Additionally, treatment will be fitted on its own in a further proportional hazards survival analysis.

Further details, including model assumptions and diagnostics to be examined are included in the study SAP. The preceding analysis will be repeated using the Per Protocol Population.

Kaplan-Meier plots will be presented by treatment and wound type, baseline ulcer area strata, ulcer duration (categorized) and also to represent all covariates with significant effects in the

final survival analysis model. Individual plots for multiple factors will be generated where appropriate.

In addition, a sensitivity analysis will be performed to ensure that the efficacy findings are not reliant on assumptions made in either the analysis or derivations. For purposes of the sensitivity analysis, the time to confirmed closure for those subjects discontinuing the treatment period prematurely, will be censored at the maximum possible duration of treatment under the study protocol (84 days), rather than time of actual discontinuation. Lastly, the two sensitivity analyses defined in the proportion of subjects achieving confirmed closure analysis will be repeated for the time to confirmed closure, in these cases the censoring flag may be modified as detailed previously, but the time in days will remain unchanged.

Change in subject reported Quality of Life (QoL)

The instruments used to assess subject reported Quality of Life will be the Cardiff Wound Impact Schedule (CWIS) and the EQ-5D.

The EQ-5D is a standardized measure of health status developed by the EuroQol Group and provides a simple measure of general health. The EQ-5D descriptive system contains 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The subject is asked to state each dimension on a scale comprising of 3 levels: no problems, some problems, or severe problems. Separately, the EQ-5D visual analog scale (EQ VAS) records the subject's self-rated health on a vertical, Visual Analog Scale (VAS). This information is used as a quantitative measure of health outcome.

In comparison, the CWIS is a measure designed to specifically assess the impact of lower limb chronic wounds on subject health-related quality of life (HRQoL) and activities of daily living (ADL). The CWIS contains four domains; Quality of life, Well-being, Physical symptoms and Daily Living (Experienced and Stressfulness of experience are two separate domains).

Both the EQ-5D and CWIS will be provided to all subjects participating in the study at the Randomization Study Visit 1 and at the End of Treatment period for completion. Missing and ambiguous values will be coded as per the relevant instrument documentation. All analyses relating to Quality of Life assessments will be performed using the Full Analysis Set.

Subject responses to individual questions at each assessment are ordinal variables and will be summarized by treatment and wound strata (and overall) using frequency distributions which will detail the number and percentage of subjects which fall into each category.
Subject responses to the EQ VAS scale and derived Time Trade-off (TTO) indexes and domain averages at each assessment are continuous variables and will be summarized by treatment and wound strata (and overall) using the following summary statistics: mean, median, standard deviation, minimum and maximum values, and number of observations.
The change in EQ VAS, derived TTO index and domain averages between the Randomization Visit and the End of Treatment period will also be summarized separately using the above continuous summary statistics. A Wilcoxon Rank-Sum test stratified by wound strata will be used to test for a difference in the change in EQ VAS between the two treatments. This analysis will be repeated separately for the change in TTO index and domain averages.

10.3.3 Exploratory Efficacy

The exploratory efficacy variables include as follows. The Presence of Infection/Clinical signs of infection, Estimation of tissue types, Condition of target ulcer peri-wound skin, Need for administration of antibiotics and additional interventions, dressing wear time, pain on removal of dressing and at initiation of, and during, therapy. In addition, the impact of the device on aspects of daily living and satisfaction with device therapy will also be assessed. In the analyses detailed in this section, the Full Analysis Set will be used.

Presence of Infection / Clinical signs of infection

A Fishers Exact test will be used to test for a difference in the percentage of subjects with incidence of infection presenting during the 12-week treatment period between treatments, the corresponding 95% confidence intervals will also be presented.

The presence of infection and clinical signs of infection will be summarized at each assessment by treatment and wound type.

Need for administration of antibiotics and additional interventions

A Fishers Exact test will be used to test for a difference in the percentage of subjects requiring either the administration of antibiotic or additional interventions, between treatments. The corresponding 95% confidence intervals will also be presented.

The need for administration of antibiotics and additional interventions will be summarized at each assessment and overall by treatment and wound type.

Dressing wear time

The linear regression model will be fitted to the average wear time per subject. Treatment, center, wound strata, baseline ulcer area and exudate level will be included in the initial model.

The difference between the two treatments in terms of average wear time per subject (treatment parameter estimate) will be presented along with the 95% confidence intervals. If residuals are found to be not normally distributed then non-parametric bootstrapping will be applied. Further information is included in the SAP.

The average wear time per subject (at a subject level) will be summarized by treatment for each of the covariates detailed in the previous paragraph. The duration of dressing wear (at a dressing level) will also be summarized by treatment, and: center, wound strata, level of exudate at the previous assessment and ulcer area (categorized) at the previous assessment.

Impact of the device on aspects of daily living and satisfaction with device therapy

All responses to the exit survey will be summarized by treatment and by individual tNPWT device. In addition, where appropriate, a Cochran-Mantel-Haenszel test will be used to test for a difference in subject response between treatments for individual survey questions.

Remaining exploratory endpoints, including the estimation of tissue types present, condition of peri-wound skin and the pain on removal of dressing and at initiation of, and during, therapy, will be summarized by assessment and treatment.

Other Planned Analysis

At minimum, all data collected will be summarized and listed by treatment; where appropriate data collected will also be summarized by tNPWT device. Additional subsets for summaries may be utilized as a result of the analyses relating to the primary and secondary objectives.

10.4 SAFETY

All safety analyses and summaries will be conducted using the Safety Population. Unless otherwise stated, all safety summaries will be presented by treatment and wound type (DFU or VLU) and overall. All safety analyses will also be separated by tNPWT device.

Extent of Exposure

The duration of treatment with NPWT will be summarized.

Adverse Events

Adverse events will be coded and grouped by system organ class using the Dictionary for Medical Drug Regulatory Activities (MedDRA).

The number of subjects reporting: adverse events, serious adverse events, severe adverse events, investigational device related adverse events, a serious investigational device related adverse event, an unexpected adverse event and a serious unexpected adverse event. In addition, for each adverse event, the following will be summarized: severity, treatment, NPWT usage, the relationship to the investigational device, the possible cause if related, outcome and duration of the resolved adverse events and the duration of the adverse events at trial discontinuation.

The proportion of subjects with a device-related adverse event will be compared between treatments using Fisher's exact test. In addition, the percentage of serious device related adverse events and the corresponding 1-sided upper 95% confidence limit will be detailed assuming a Poisson distribution for serious device related adverse events separately for each treatment.

The number and proportion of subjects reporting treatment-emergent adverse events split by treatment separately by system organ class, and preferred term will be summarized by:

1. Their relationship with the investigational device (not related or related). If the relationship is missing, the adverse event will be assumed to be treatment-related and a footnote will be added to the table. If a subject experiences more than one preferred term within a system organ class, then the relationship at the system organ class level for that subject will be reported according to their most related relationship for each preferred term.

2. The severity of the adverse event (mild, moderate or severe).

3. Whether or not the adverse event is serious

4. The adverse event outcome.

5. Whether or not the adverse event is expected or unexpected.

Clinical Laboratory Evaluations

The subject blood biochemistry and hematological parameters (including the numbers of subjects that are below, within and above the normal ranges) at screening visit will be summarized.

Vital Signs, Physical Findings

The subject blood pressure (systolic and diastolic), pulse and temperature at the screening visit will be summarized.

11. SAMPLE SIZE JUSTIFICATION

The study is intended to test for non-inferiority in the percentage change in target ulcer area between PICO and tNPWT over a 12-week treatment period. During a review of five previous studies with venous leg ulcer and diabetic foot ulcer, with treatment of PICO or tNPWT, the mean percentage change in ulcer area was found to be approximately between 47-62%, in cases where it was considered an appropriate measure, the standard deviation ranged approximately between 21-24.5%. Using a non-inferiority margin of 12.5%, a sample size of 128 subjects will provide 80% statistical power at the (cumulative) 0.025 one-sided significance level assuming a weighted average mean healing of 60% with a worst case standard deviation of 24.5%. To allow for a 20% drop out rate throughout the 12-week treatment period, a total of approximately 160 subjects (80 per treatment) will be randomized.

The sample size randomized will include a minimum of 100 VLU to allow for a minimum of 70% power for VLU-only analysis using the above assumptions.

An interim analysis (built into the sample size) of key variables will take place after approximately 50% of target recruitment (80 subjects completed) with the stipulation that the interim will contain at least 40 VLU and 20 DFU. The interim analysis will contain a check for efficacy with an alpha spend of 0.002. A non-binding look for futility will also be performed at the same time point. The Lan and DeMets (1983) "Pocock" spending function will be used[24]. If the efficacy boundary of 2.963, using the Z scale is exceeded ($Z>2.963$) a recommendation will be made to terminate the trial on the basis of efficacy. Alternatively, if the futility bound of 0.559 using the Z scale is crossed ($Z<0.559$) it will be recommended to terminate the trial prematurely due to lack of efficacy (futility). Further details regarding the stopping criteria, including the corresponding values on the p-value scale to be used in circumstances where distributional assumptions do not hold, can be found in the SAP.

12. ADVERSE EVENTS

12.1 GENERAL INFORMATION

An Adverse Event (AE) is any untoward medical occurrence temporally associated with the use of an investigational medicinal product or device, whether or not considered causally related to that product/device. An AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease.

An Adverse Device Effect (ADE) is an adverse event that, in the opinion of the investigator, is related to the device.

12.2 SERIOUS ADVERSE EVENTS

An adverse event is considered "serious" if, in the view of either the investigator or the sponsor, it

- Results in death
- Is life-threatening (*NOTE*: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the subject was at risk of death at the time of the

event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)

- Requires in subject hospitalization or results in prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

A DevD is a malfunction of the device that could present a risk to the subject, caregiver, or bystander.

12.3 NON-SERIOUS ADVERSE DEVICE EFFECTS

A nonserious adverse event is defined as a change from baseline (pre-treatment) in a subject's medical health that is not life-threatening, does not require hospitalization, does not prolong a current hospitalization and is not disabling. Nonserious adverse device effects must be reported to Smith & Nephew Inc., by use of an Adverse Event Form.

All nonserious adverse events must be reported in the subject's source documents; AE associated with the target ulcer or related to the test article must be recorded on an Adverse Event Form regardless of whether or not they are considered to be related to the test article

12.4 REPORTING AND EVALUATION AE AND SAE

AE associated with the target ulcer and target leg and all SAE, SADE, UADE and ADE of any kind will be recorded in the AE eCRF; DevD will be recorded on an eCRF specifically designed for recording such events. The Investigator will evaluate all SAE and target ulcer and target leg AE for relationship to the device and severity. AE judged to be device related and all SAE will be entered into the eCRF. All device-related AE, SADE, SAE and DevD will also be reported in the SAE form available in the Regulatory Folder and faxed to the Clinical Study Manager, Medical Monitor, and Medical Reviewer within 24 hours of knowing about the event (Figure 12.4-1). Target ulcer and target leg AE judged not related to the device will be entered into the safety database within 48 hours of becoming aware of the event. All SAE and device related AE will be reviewed by the Medical Monitor and the Medical Reviewer to determine which, if any, meet expedited reporting criteria.

All events requiring expedited reporting will be forwarded to Regulatory by the Medical Reviewer for further processing.

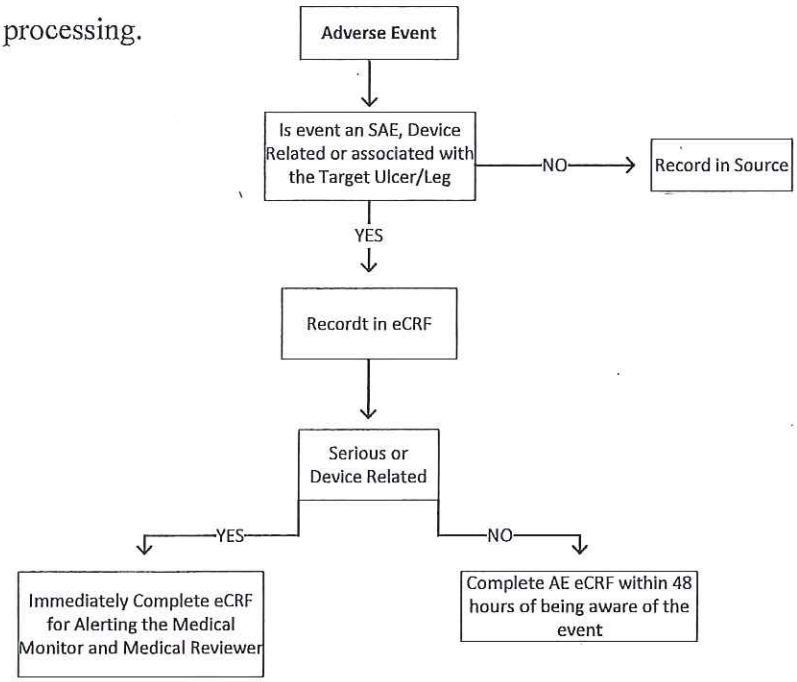


Figure 12.4-1: Evaluation of an Adverse Event by the Investigator

All DevD are considered to be serious and will be reported within 24 hours to the Sponsor

When new significant follow up information is obtained as well as when the outcome of an event is known, the Investigator must update the appropriate eCRF forms with the additional information. In certain cases, Smith & Nephew Inc. also may request a letter from the Investigator that summarizes the events related to the case.

The Medical Monitor and Medical Reviewer will review and classify all devices related AE and all SAE as follows, based on FDA 21 CFR §812.40:

Adverse Device Effect (ADE) Adverse event is judged to be device related, but is not serious and does not meet expedited reporting

Unanticipated Adverse Device Effect (UADE) Any serious adverse event that is caused by or related to the investigational device, not previously identified in nature, severity or degree; this meets the criteria for expedited reporting and the Sponsor will forward to the Regulatory group for submission to the FDA within 15 days of the initial report from the site.

Serious Adverse Event (SAE) A serious adverse event that is not related to the use of the device does not meet the criteria for expedited reporting.

Device Deficiency (DevD) A malfunction of the device that could present a risk to the subject, caregiver, or bystander. This is reportable if the malfunction has the chance of causing a death or serious injury if a recurrence of the malfunction is not remote.

Device–related AE and all SAE of any kind must be reported to the following Smith & Nephew representatives within 24 hours of the Investigator's knowledge of the event:

Table 12.4-1: Contact Information for Reporting of Unanticipated Adverse Device Effects

Alain Rohan, MBBS, MPH Medical Reviewer Director Product Surveillance & Information	Business Phone Business Fax	817-302-3902 817-887-0721

	Mobile Phone	817-751-0053
Innes Cargill, PhD Medical Monitor Director Clinical Data and Documentation	Business Phone	817-302-3913
	Business Fax	817-887-0721
	Mobile Phone	254-681-1010

12.5 Adverse Device Effect Severity and Causality Assessment

The severity of all AE, will be assessed by the Principal Investigator and should be classified as mild, moderate, or severe. The classification should be based on the following definitions:

- **Mild** – An event is mild if the subject is aware of, but can easily tolerate the sign or symptom;
- **Moderate** – An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities;
- **Severe** – An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

In addition, the Principal Investigator will determine causality according to the following definitions:

- **Not Related** – An AE is considered to be not related to the use of the device when the effect is DEFINITELY UNRELATED or UNLIKELY to have any relationship to the use of the device;
- **Related** – An AE is considered to be related to the use of the device when there is a POSSIBLE, PROBABLE, or DEFINITE relationship between the AE and the use of the device.

All ADE and UADE are considered to be related to the use of the device.

12.6 Unblinding of Test Article

Not Applicable.

12.7 FOLLOW-UP OF SUBJECTS WITH ADVERSE EVENTS

For subjects who are experiencing ongoing unresolved AE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit in order to determine the outcome of the event. Any additional data must be documented and available to the sponsor who will determine when the data need to be documented on the case report forms.

13. INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with the commitments outlined in the Statement of Investigator (Form FDA 1572) and with Good Clinical Practices (GCP) and with all applicable regulatory requirements as outlined in Appendix18.6 of this protocol.

14. SPONSOR AND MONITOR RESPONSIBILITIES

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that: the rights and well being of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; and the study is conducted in compliance with the current approved protocol [and amendment(s), if applicable], with current GCP, and with applicable regulatory requirements.

All studies will have a site initiation. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written and fax correspondence. The Study Manager and/or assigned study monitor will contact each site at appropriate intervals. The Study Manager will determine the frequency of site visits. Close-out visits will take place after the last visit of the last subject.

15. CONFIDENTIALITY OF THE STUDY

The confidentiality of this study and associated documents is governed by the terms of the Clinical Trial Agreement.

16. REFERENCES

1. Schwartz J *et al.*,(2015). Single use negative pressure wound therapy for the treatment of chronic lower leg wounds. Journal of Wound Care, Vol. 24., No. 2, February, 2015.
2. Agale, SV., (2013). Review Article. Chronic Leg Ulcers: Epidemiology, Aetiopathogenesis, and Management. Ulcers, Volume 2013 (2013).
3. Nelzen O *et al.*, (2009). The prevalence of chronic lower limb ulceration has been underestimated: results of a validated population questionnaire. British Journal of Surgery; 83(2), ; 255-58, February, 1996, in Wound Care Essentials, Baranoski S and Ayello EA, Chapter 14. Venous Disease and Lymphedema Management. Wolters Kluwer Health. 3rd Edition.
4. Singh N, Armstrong DG, Lipsky BA (2005) Preventing foot ulcers in patients with diabetes. JAMA 293: 217-228.
5. Boulton AJM, Kirsner RS, Vileikyte L (2004) Neuropathic Diabetic Foot Ulcers. N Engl J Med 351: 48-55.
6. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJM (2003) Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-hispanic whites from a diabetes disease management cohort. Diabetes Care 26: 1435-1438.
7. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, et al. (2014) Diabetic foot ulcers. Part II. Management. J Am Acad Derm 70: 21.e1-24.
8. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W (1997). Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg. 1997 Jun;38(6):553-62.
9. Argenta LC, Morykwas MJ. Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. Ann Plast Surg. 1997 Jun;38(6):563-76; discussion 577.

10. Dorafshar, A. H., Franczyk, M., Gottlieb, L. J., Wroblewski, K. E. and Lohman, R. F. A; Prospective Randomized Trial Comparing Subatmospheric Wound Therapy With a Sealed Gauze Dressing and the Standard Vacuum-Assisted Closure Device. Annals of plastic surgery 69, 79–84 (2012).

11. Rahmanian-Schwarz, A., Willkomm, L.-M., Gonser, P., Hirt, B. and Schaller, H.-E.; A novel option in Negative Pressure Wound Therapy (NPWT) for chronic and acute wound care. Burns: Journal of the International Society for Burn Injuries 38, 573–7 (2012).

12. Armstrong, D. G., Marston, W. a, Reyzelman, A. M. and Kirsner, R. S. Comparative effectiveness of mechanically and electrically powered Negative Pressure Wound Therapy devices: A multicenter randomized controlled trial. Wound repair and regeneration: official publication of the Wound Healing Society [and] the European Tissue Repair Society 20, 332–41 (2012).

13. Hudson DA, Adams KG, Huyssteen A Van, Martin R, Huddleston EM. Simplified negative pressure wound therapy: clinical evaluation of an ultraportable, no-canister system. International Wound Journal, 2013

14. Canonico S, Campitiello F, Della Corte A, Padovano S, Giannini S, Luciani D, et al. Therapeutic possibilities of portable NPWT. Acta Vulnologica. 2012;10(2):57–64.

15. Hurd T, Trueman P, Rossington A. Use of a portable, single-use negative pressure wound therapy device in home care patients with low to moderately exuding wounds: a case series. Ostomy Wound Manage. 2014;60:30–6.Mendonca D a, Drew PJ, Harding KG, Price PE. A pilot study on the effect of topical negative pressure on quality of life. Journal of wound care. 2007 Feb;16(2):49–53.

16. Krug E, Berg L, Lee C, Hudson D, Birke-Sorensen H, Depoorter M, Dunn R, Jeffery S, Duteille F, Bruhin A, Caravaggi C, Chariker M, Dowsett C, Ferreira F, Martínez JM, Grudzien G, Ichioka S, Ingemansson R, Malmsjo M, Rome P, Vig S, Runkel N; International Expert Panel on Negative Pressure Wound Therapy [NPWT-EP]. Martin R, Smith J. Evidence-based recommendations for the use of Negative Pressure Wound

Therapy in traumatic wounds and reconstructive surgery: steps towards an international consensus. Injury. 2011 Feb;42 Suppl 1:S1-12. Review

17. Birke-Sorensen H, Malmsjo M, Rome P, Hudson D, Krug E, Berg L, Bruhin A, Caravaggi C, Chariker M, Depoorter M, Dowsett C, Dunn R, Duteille F, Ferreira F, Francos Martínez JM, Grudzien G, Ichioka S, Ingemansson R, Jeffery S, Lee C, Vig S, Runkel N; International Expert Panel on Negative Pressure Wound Therapy [NPWT-EP], Martin R, Smith J. Evidence-based recommendations for negative pressure wound therapy: treatment variables (pressure levels, wound filler and contact layer)--steps towards an international consensus. J Plast Reconstr Aesthet Surg. 2011 Sep;64 Suppl:S1-16. Review.

18. Vig S, Dowsett C, Berg L, Caravaggi C, Rome P, Birke-Sorensen H, Bruhin A, Chariker M, Depoorter M, Dunn R, Duteille F, Ferreira F, Martínez JM, Grudzien G, Hudson D, Ichioka S, Ingemansson R, Jeffery S, Krug E, Lee C, Malmsjo M, Runkel N; International Expert Panel on Negative Pressure Wound Therapy [NPWT-EP], Martin R, Smith J. Evidence-based recommendations for the use of negative pressure wound therapy in chronic wounds: steps towards an international consensus. J Tissue Viability. 2011 Dec;20 Suppl 1:S1-18. Epub 2011Nov 25

19. Mouës CM, Van den Bemd GJCM, Meerding WJ, Hovius SER. An economic evaluation of the use of TNP on full-thickness wounds. Journal of wound care. 2005 May;14(5):224–7.

20. Braakenburg A, Obdeijn MC, Feitz R, Van Rooij I a LM, Van Griethuysen AJ, Klinkenbijl JHG. The clinical efficacy and cost effectiveness of the vacuum-assisted closure technique in the management of acute and chronic wounds: a randomized controlled trial. Plastic and reconstructive surgery. 2006 Aug;118(2):390–7; discussion 398–400.

21. Armstrong DG, Marston W a, Reyzelman AM, Kirsner RS. Comparison of negative pressure wound therapy with an ultraportable mechanically powered device vs. traditional electrically powered device for the treatment of chronic lower extremity ulcers: a multicenter randomized-controlled trial. Wound Repair Regen. 2010;19(2):173–80.

22. Marston WA., Armstrong DG, Reyzelman AM, Kirsner RS. A Multicenter Randomized Controlled Trial Comparing Treatment of Venous Leg Ulcers Using Mechanically Versus Electrically Powered Negative Pressure Wound Therapy. Adv Wound Care. 2014 Oct 16;00(00):141016081615000.

23. Lan, KKG and DeMets, DL (1983), Discrete sequential boundaries for clinical trials. *Biometrika*; 70: 659-663.

24. Price PE and Harding KG (2004) The Cardiff Wound Impact Schedule: the development of a condition specific questionnaire to assess health-related quality of life in patients with chronic wounds. International Wound Journal 1(1):10-17

17. STUDY PLAN

Table 17-1: Study Procedures by Treatment Plan

Parameter	Screening Run-in Period		Treatment Period Weekly Visits (±1 day)		End of Treatment Weekly Visits	
Trial Visit	Screen/Run-in Visit 1	Screen/Run-in Visit 2	Study Visit 1	Study Visits 2 to 12	Study Visit 13[c]	Study Visit 14
Informed Consent	X					
Quality of Life Questionnaires (CWIS, EQ-5D)			X	X[d]	X[d]	X[e]
Register with sealedenvelope (IWR)	X	X				
Demography	X					
Inclusion/Exclusion Criteria	X	X				
Medical Hx Including Ulcer Disease Hx	X					
Physical Exam including Vital Signs	X					
Selection of Target Ulcer	X					
VAS Pain Assessments	X	X	X	X	X	X[e]
Examine Target Ulcer for infection	X	X		X		
Photography and Measure Ulcer Size	X	X		X	X	X
Great Toe Pressure or ABI (or $TcPO_2$)	X					
Blood collection for hematology, chemistry, pre-albumin and HbA_{1c}	X					
Urine Pregnancy Test	X[a]					X[a]
Randomization			X[b]			
Application of NPWT & Device questions			X	X		
Target ulcer & peri-wound assessment			X	X	X	X
Ulcer Care	X	X	X	X	X	
Subject Satisfaction Questionnaire						X
Assessment of Adverse Events or DevD	X	Assessed throughout the trial				
Concomitant Medications	X	Assessed throughout the trial				

a If subject is female of child-bearing potential, a pregnancy test is required.
b Subjects will be randomized only after the Investigator has verified that all inclusion/exclusion criteria are met.
c Subject's target ulcer judged to have not closed at Visit 13 will not complete the procedures for this Visit, but will complete the End of Treatment Assessment or Early Discontinuation Visit 14 procedures.
d Subjects to complete CWIS and EQ-5D only if the target ulcer is closed or will be surgically closed during the treatment period.
e Subjects to complete CWIS, EQ-5D and VAS assessments only if the target ulcer remained open during the treatment period.

18. APPENDICES

18.1 CONTRAINDICATIONS TO NEGATIVE PRESSURE WOUND THERAPY (NPWT)

The use of PICO is contraindicated in the presence of:

- Subjects with malignancy in the wound bed or margins of the wound (except in palliative care to enhance quality of life).
- Previously confirmed and untreated osteomyelitis.
- Necrotic tissue with eschar present.
- Exposed arteries, veins, nerves or organs.
- Anastomotic sites.
- Emergency airway aspiration.
- Pleural, mediastinal or chest tube drainage.
- Surgical suction.

The use of tNPWT is contraindicated in the following:

- Placing foam dressings directly in contact with exposed blood vessels, anastomotic sites, organs, or nerves.
- Malignancy in the wound
- Untreated osteomyelitis
- Non-enteric and unexplored fistulas
- Necrotic tissue with eschar present
    - NOTE: After debridement of necrotic tissue and complete removal of eschar, tNPWT may be used.

18.2 ARANZ SILHOUETTE

Silhouette is a portable device that easily allows capture of information about a subject's ulcer, which is analyzed, managed, and stored in a central database. Information captured includes photographic images, quantitative measures, and other ulcer assessment data input by the clinician, all obtained with no subject contact. Silhouette builds that information into an electronic record for printing, electronic uploading to the Sponsor's database, and archiving. Information about the ulcer's measurement history is available on this system so that the serial progression of wound status can be calculated and presented. Most of this process is automated.

18.3 ROUTINE LABORATORY TESTS

The following laboratory tests will be performed at the Screening visit to confirm eligibility:

Hematology: Red Blood Cell (RBC) count, Hemoglobin, Hematocrit, Platelets, White Blood Cell (WBC) total count, and differential (%) including absolute counts (x 10^9/L)

Blood Biochemistries: Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin, Total Protein, Urea, Glucose, and HbA_{1c}

Additional Chemistries: Pre-albumin

Urine Pregnancy Test to be performed at Screening Run-in Visit 1 & Exit Visit *(only for females that are not premenarchal, not postmenopausal, or surgically sterile)*

18.4 VISUAL ANALOGUE SCALE (VAS) FOR PAIN

The Visual Analogue Scale is simply a line of fixed length, on which the subject marks their subject experience of pain with a single stroke using a pen.

At each specified visit the degree of pain associated with removal of the dressing, application of the NPWT and dressing wear to the target leg will be assessed using a visual analog scale (VAS). The subject will record their level of pain on a 100 mm visual analog scale, similar to the one illustrated above. The scale will be marked 'no pain' on the left side of the scale and 'severe pain' at the right end of the scale. The subject will be instructed to place a vertical mark on the scale, using a black ball-point pen, indicating their level of pain at the visit.

The Investigator, or designee, will measure the distance (in millimeters) from the left end of the VAS line to the vertical line drawn by the subject. This value will be entered in the subject's CRF as a measure of the pain associated with the target ulcer.

18.5 EQ-5D

The EQ-5D-5L still consists of 2 pages – the EQ-5D-5L descriptive system and the EQ visual Analogue scale (EQ VAS). The descriptive system comprises the same 5 dimensions as the EQ-5D-5D-3L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY
- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE
- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

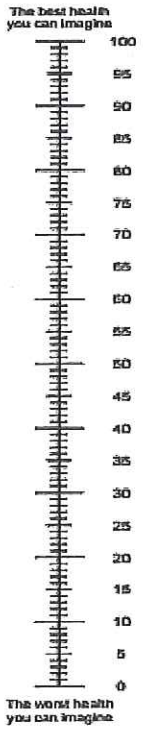
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

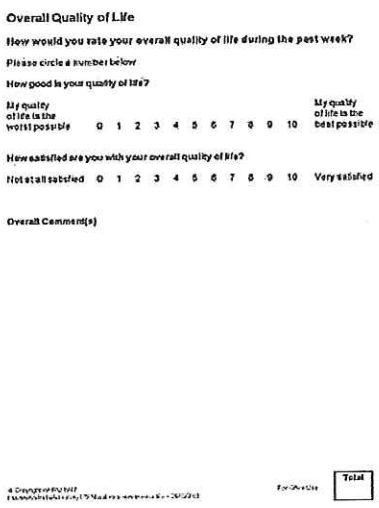
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



18.6 CWIS[25]

The C.W.I.S. is a condition-specific quality of life tool that has been developed at the Wound Healing Research Unit in Cardiff. The tool has undergone extensive piloting to establish the psychometric properties of the tool. The tool gives a profile of scores for Well-Being, Physical Symptoms and Daily Living and Social Life. Physical Symptoms and Daily Living, and Social Life are assessed for both the experience of a given symptom and the associated stress experienced by the individual. In addition, an indication of overall HRQoL is assessed using a global scale, together with an indication of the satisfaction with that HRQoL.



Overall Quality of Life

How would you rate your overall quality of life during the past week?

Please circle a number below

How good is your quality of life?

My quality of life is the worst possible 0 1 2 3 4 5 6 7 8 9 10 My quality of life is the best possible

How satisfied are you with your overall quality of life?

Not at all satisfied 0 1 2 3 4 5 6 7 8 9 10 Very satisfied

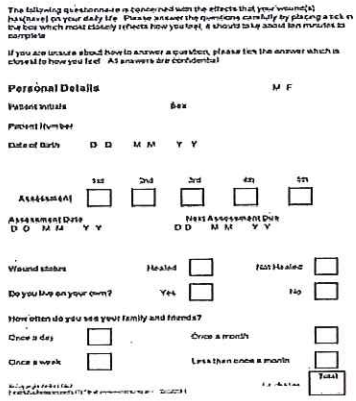
Overall Comment(s)

Total

Wound Healing Research Unit

University of Wales College of Medicine

Cardiff Wound Impact Schedule



The following questionnaire is concerned with the effects that your wound(s) has/have] on your daily life. Please answer the questions carefully by placing a tick in the box which most closely reflects how you feel. It should take about ten minutes to complete

If you are unsure about how to answer a question, please tick the answer which is closest to how you feel. All answers are confidential

Personal Details

M F

Patient initials Sex

Patient number

Date of birth D D M M Y Y

1st 2nd 3rd 4th 5th

Assessment

Assessment Date D D M M Y Y

Next Assessment Date D D M M Y Y

Wound status Healed Not Healed

Do you live on your own? Yes No

How often do you see your family and friends?

Once a day Once a month

Once a week Less then once a month

Total

Social Life

How stressful has this experience been for you?

	Not at all/ Not applicable	Slightly	Moderately	Quite a bit	Very
Difficulty getting out and about					
Relying more on others					
Your family/friends being overprotective					
Unable to enjoy your usual social life (eg hobbies)					
Limited contact with family/friends					
Not going out for fear of bumping your wound site					
Wanting to withdraw from people					

Total

Social Life

Have you experienced any of the following during the past week?

	Not at all/ Not applicable	Seldom	Sometimes	Frequently	Always
Difficulty getting out and about					
Relying more on others					
Your family/friends being over protective					
Unable to enjoy your usual social life (eg hobbies)					
Limited contact with family/friends					
Not going out for fear of bumping your wound site					
Wanting to withdraw from people					

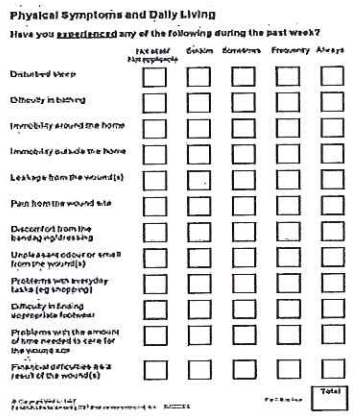
Total

Well-being

To what extent do you agree/disagree with the following statements?

	Strongly Disagree	Disagree	Not Sure	Agree	Strongly Agree
I feel anxious about my wound(s)					
I feel frustrated at the time it is taking for the wound(s) to heal					
I am confident that the wound(s) I have will heal					
I worry that I may get another wound in the future					
The appearance of the wound site is upsetting					
I feel anxious about bumping the wound site					
I worry about the impact of the wound(s) on my family/friends					

Total



Physical Symptoms and Daily Living

Have you experienced any of the following during the past week?

	Not at all/ Not applicable	Seldom	Sometimes	Frequently	Always
Disturbed sleep					
Difficulty in bathing					
Immobility around the home					
Immobility outside the home					
Leakage from the wound(s)					
Pain from the wound site					
Discomfort from the bandaging/dressing					
Unpleasant odour or smell from the wound(s)					
Problems with everyday tasks (eg shopping)					
Difficulty in finding appropriate footwear					
Problems with the amount of time needed to care for the wound site					
Financial difficulties as a result of the wound(s)					

Total

Physical Symptoms and Daily Living

How stressful has this experience been for you?

	Not at all/ Not applicable	Slightly	Moderately	Quite a bit	Very
Disturbed sleep					
Difficulty in bathing					
Immobility around the home					
Immobility outside the home					
Leakage from the wound(s)					
Pain from the wound site					
Discomfort from the bandaging/dressing					
Unpleasant odour or smell from the wound(s)					
Problems with everyday tasks (eg shopping)					
Difficulty in finding appropriate footwear					
Problems with the amount of time needed to care for the wound site					
Financial difficulties as a result of the wound(s)					

Total

18.7 IMPACT OF THE DEVICE ON ASPECTS OF DAILY LIVING AND SATISFACTION WITH DEVICE THERAPY

Subject response to a custom questionnaire to assess the impact of treatment with the device on subject's daily activities and satisfaction with the device.

Activities of Daily Living

1. It was a burden to come to the wound care clinic for my dressing change.
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
2. The use of the NPWT device restricted many of my normal activities (i.e., sleeping, walking, eating, cleaning, moving around, etc.).
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
3. The NPWT device was cumbersome and interfered with my mobility.
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
4. I was able to work and do my normal daily activities while being treated with the NPWT device.
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
5. The NPWT device was easy to use.
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
6. The NPWT device was light-weight and portable.
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
7. I wish the NPWT device was more light-weight and portable.
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
8. After treatment with the NPWT, how did your overall activity level change?
    a. Less Active/Stayed the Same/More Active

Noise from the device

1. The noise from the NPWT device was bothersome.
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
2. How often did the noise from the NPWT device bother you?
    a. Never/Rarely/Several times per day/Most of the time/All of the time

Sleep Disruption

1. The use of the NPWT device was disruptive to my sleep.
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
2. Did the noise from the NPWT device bother you when you were trying to go to sleep?
    a. Never/1–2 nights per week/2–4 nights per week/4–6 nights per week/Every night
3. How often did the use of the NPWT device disrupt your sleep?
    a. Never/1–2 nights per week/2–4 nights per week/4–6 nights per week/Every night
4. I often had to turn off the device to try and go to sleep?
    a. Never/1–2 nights per week/2–4 nights per week/4–6 nights per week/Every night

Discomfort

1. The NPWT was comfortable to wear?
    a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree
2. What was your overall discomfort while using the NPWT device?
    a. No discomfort/minimal discomfort/low level of discomfort/moderate level of discomfort/high level of discomfort

Perceived Effectiveness/Satisfaction

1. The use of the NPWT device helped my ulcer heal faster?

a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree

2. I would use the NPWT device again on another wound in the future?

   a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree

3. I am overall satisfied with the NPWT device used to treat my ulcer?

   a. Strongly Disagree/Disagree/Neutral/Agree/Strongly Agree

18.8 WOUND ASSESSMENT SCORING TOOL (BWAT-M)

1. **Undermining**: Assess by inserting a cotton tipped applicator under the wound edge; advance it as far as it will go without using undue force; raise the tip of the applicator so it may be seen or felt on the surface of the skin; mark the surface with a pen; measure the distance from the mark on the skin to the edge of the wound. Continue process around the wound. Then use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to help determine percent of wound involved.

2. **Necrotic Tissue Type**: Pick the type of necrotic tissue that is predominant in the wound according to color, consistency and adherence using this guide

White/gray non-viable tissue	=	May appear prior to wound opening; skin surface is white or gray.
Non-adherent, yellow slough	=	Thin, mucinous substance; scattered throughout wound bed; easily separated from wound tissue.
Loosely adherent, yellow slough	=	Thick, stringy, clumps of debris; attached to wound tissue.
Adherent, soft, black eschar	=	Soggy tissue; strongly attached to tissue in center or base of wound.
Firmly adherent, hard/black eschar	=	Firm, crusty tissue; strongly attached to wound base and edges (like a hard scab).

3. **Necrotic Tissue Amount**: Use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to help determine percent of wound involved.

4. **Exudate Type**: Before assessing exudate type, gently cleanse wound with normal saline. Pick the exudate

type that is predominant in the wound according to color and consistency, using this guide:

Bloody	=	Thin, bright red
Serosanguinous	=	Thin, watery pale red to pink
Serous	=	Thin, watery, clear
Purulent	=	Thin or thick, opaque tan to yellow
Foul purulent	=	Thick, opaque yellow to green with offensive odor

5. **Exudate Amount**: Use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to determine percent of wound area involved with exudate. Use this guide:

None	=	Wound tissues dry.
Scant	=	Wound tissues moist; no measurable exudate.
Small	=	Wound tissues wet; moisture evenly distributed in wound; drainage involves < 25% dressing.
Moderate	=	Wound tissues saturated; drainage may or may not be evenly distributed in wound; drainage involves > 25% to < 75% dressing.
Large	=	Wound tissues bathed in fluid; drainage freely expressed; may or may not be evenly distributed in wound; drainage involves > 75% of dressing.

6. **Skin Color Surrounding Wound:** Assess tissues within 4cm of wound edge. Dark-skinned persons show the colors "bright red" and "dark red" as a deepening of normal ethnic skin color or a purple hue. As healing occurs in dark-skinned persons, the new skin is pink and may never darken.

7. **Granulation Tissue:** Granulation tissue is the growth of small blood vessels and connective tissue to fill in full thickness wounds. Tissue is healthy when bright, beefy red, shiny and granular with a velvety appearance. Poor vascular supply appears as pale pink or blanched to dull, dusky red color.

8. **Epithelialization:** Epithelialization is the process of epidermal resurfacing and appears as pink or red skin. In partial thickness wounds it can occur throughout the wound bed as well as from the wound edges. In full thickness wounds it occurs from the edges only. Use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to help determine percent of wound involved and to measure the distance the epithelial tissue extends into the wound.

Item	Assessment
1. Undermining	1 = None present 2 = Undermining < 2 cm in any area 3 = Undermining 2-4 cm involving < 50% wound margins 4 = Undermining 2-4 cm involving > 50% wound margins 5 = Undermining > 4 cm or Tunneling in any area
2. Necrotic Tissue Type	1 = None visible 2 = White/grey non-viable tissue &/or non-adherent yellow slough 3 = Loosely adherent yellow slough 4 = Adherent, soft, black eschar 5 = Firmly adherent, hard, black eschar
3. Necrotic Tissue Amount	1 = None visible 2 = < 25% of wound bed covered 3 = 25% to 50% of wound covered 4 = > 50% and < 75% of wound covered 5 = 75% to 100% of wound covered
4. Exudate Type	1 = None 2 = Bloody 3 = Serosanguinous: thin, watery, pale red/pink 4 = Serous: thin, watery, clear 5 = Purulent: thin or thick, opaque, tan/yellow, with or without odor
5. Exudate Amount	1 = None, dry wound 2 = Scant, wound moist but no observable exudate 3 = Small 4 = Moderate 5 = Large
6. Skin Color Surrounding Wound	1 = Pink or normal for ethnic group 2 = Bright red &/or blanches to touch 3 = White or grey pallor or hypopigmented 4 = Dark red or purple &/or non-blanchable 5 = Black or hyperpigmented
7. Granulation Tissue	1 = Skin intact or partial thickness wound 2 = Bright, beefy red; 75% to 100% of wound filled &/or tissue overgrowth 3 = Bright, beefy red; < 75% & > 25% of wound filled 4 = Pink, &/or dull, dusky red &/or fills < 25% of wound 5 = No granulation tissue present

Item	Assessment
8. Epithelialization	1 = 100% wound covered, surface intact 2 = 75% to < 100% wound covered &/or epithelial tissue extends to > 0.5 cm into wound bed 3 = 50% to < 75% wound covered &/or epithelial tissue extends to < 0.5 cm into wound bed 4 = 25% to < 50% wound covered 5 = < 25% wound covered

18.9 RECOMMENDED PICO DRESSINGS BASED ON WOUND AREA

Dressing sizes

Dressing Size	Pad Size	Pad Area
cm	cm	cm^2
10 * 20	5 * 15	75
10 * 30	5 * 30	125
15 * 15	10 * 10	100
15 * 20	10 * 15	150
15 * 30	10 * 25	250
20 * 20	15 * 15	225

Wound size constraints with "2cm border" recommendation

Maximum wound Length	Maximum wound width	Maximum wound Area if low exudate	Maximum wound Area if moderate exudate
cm	cm	cm^2	cm^2
11	1	11	18.75
26	1	26	31.25
6	6	36	25
11	6	66	37.5
21	6	126	62.5
11	11	121	56.25

18.10 MID- TO SUPERPOTENT CORTICOSTEROIDS

rINN Name	Do not use	rINN Name	Do not use
Amcinonide	≥ 0.10%	Fluocinonide	≥ 0.05%
Betamethasone benzoate	≥ 0.025%	Flurandrenolide	≥ 0.05%
Betamethasone dipropionate	≥ 0.05%	Fluticasone propionate	≥ 0.005%
Betamethasone valerate	≥ 0.01%	Halcinonide	≥ 0.10%
Clobetasol propionate	≥ 0.05%	Halobetasol propionate	≥ 0.05%
Clocortolone pivalate	≥ 0.10%	Hydrocortisone valerate	≥ 0.20%

Desoximetasone	≥ 0.05%	Mometasone furoate	≥ 0.10%
Diflorasone diacetate	≥ 0.05%	Triamcinolone acetonide	≥0.025%
Fluocinolone acetonide	≥ 0.01%		

18.11 CURRENT SPONSOR-APPROVED TNPWT DEVICES

The following devices are approved by the Sponsor for use as the tNPWT comparator arm. Other tNPWT device not listed below will need approval by the Sponsor before its use on a subject.

- ActiV.A.C.® Negative Pressure Wound Therapy (NPWT) System, Kinetic Concepts, Inc., (KCI) an Acelity Company, San Antonio, TX.
- Invia® Liberty Negative Pressure Wound Therapy (NPWT) System, Medela, Inc., McHenry, IL.
- Avance® Negative Pressure Wound Therapy (NPWT) System, Mölnlycke Health Care, Göteborg, Sweden
- Renasys◊ Negative Pressure Wound Therapy (NPWT) System, Smith & Nephew, Inc., Fort Worth, TX. – For use only in countries where clearance from the appropriate regulatory authorities has been received

18.12 PRINCIPAL INVESTIGATOR OBLIGATIONS

References: ICH Guidelines for Good Clinical Practice (E6), and Code of Federal Regulations, 21 CFR, Parts 50, 54, 56, 312, 812.

The Principal Investigator(s) must:

1. Study Participants

Ensure the protection of the rights, safety, and well being of the study participants.

2. Qualifications

Be qualified by education, training, and experience to assume responsibility for the proper conduct of the study and provide documented evidence of such qualifications.

3. Protocol

Be thoroughly familiar with the Protocol, Protocol Amendment(s), and Clinical Investigators Brochure (CIB), and usage of the test article throughout the duration of the clinical study.

a. Sign the protocol agreeing to conduct the study according to the protocol.
b. Document and explain deviations from the protocol to the Sponsor and IRB/IEC, as required.
c. Inform the Sponsor and IRB/IEC within 24 hours if a protocol deviation is required to protect the safety of the subject.

4. Resources and Staff

Secure sufficient resources to conduct the study.

a. Devote sufficient time to properly conduct and complete the clinical study.
b. Oversee and assume responsibility for all sub-Investigators and site study personnel; assure that they are adequately trained and informed about the study protocol and investigational product; maintain a list of their delegated study-related activities.
c. Ensure that all instruments and equipment used in the study are maintained in good working order.

5. Regulatory Requirements

Comply with all applicable regulatory requirements to ensure Good Clinical Practice (GCP).

6. Study Participant Recruitment

Recruit, or demonstrate the appropriate effort to recruit, the required number of eligible study participants within the agreed recruitment period, based upon the established medical indication and the inclusion/exclusion criteria in the protocol.

7. Institutional Review Board / Independent Ethics Committees

Obtain written approval for the protocol (including protocol amendments) and the informed consent form (including informed consent revisions) from the Institutional Review Board (IRB) / Independent Ethics Committee (IEC).

a. Obtain IRB/IEC approval of subject recruitment materials and/or medium and any other information to be provided to potential study participants (e.g., instructions, brochures).
b. Submit copies of the IRB/IEC approval(s) to the Sponsor.
c. Obtain the name and address of the IRB/IEC and the membership roster or "Statement of Membership" from the IRB/IEC chairperson.
d. Maintain all records and correspondence to and from the IRB/IEC.
e. Submit periodic progress and final reports to the IRB/IEC at the frequency required by the IRB/IEC (at least yearly).
f. Obtain re-approval from the IRB/IEC as required.
g. Obtain IRB/IEC re-approval of revised Informed Consent documents and all applicable protocol amendments before their implementation.
h. Ensure that the IRB/IEC is organized and operates according to GCP and other applicable regulatory requirements.

8. Informed Consent/Assent

Obtain written informed consent and/or assent from each study participant (or legal representative) using the current IRB/IEC-approved Informed Consent Form (ICF) before performing any study-specific procedures on the study participant.

a. Ensure that the IRB/IEC-approved ICF is fully executed, including appropriate signatures, dates and other information.
b. Ensure that the written informed consent and any other written information to be provided to study participants is revised, approved by the IRB/IEC, disseminated to each study participant (or legal representative), and fully executed (including appropriate signatures, dates and other information) when new information becomes available that may be relevant to the study participant's consent.

9. Adverse Events

Report all adverse events to the Sponsor as specified in the protocol.

a. Ensure adequate medical care is provided to a subject for any adverse event.
b. Report all SAE and device related AE and Dev D to the Sponsor within 24 hours of the investigator becoming aware of the occurrence.
c. Report all SAE and device-related AE or DevD to the IRB/IEC according to regulatory and IRB/IEC requirements
d. Clinical investigators and ultimately the Principal Investigator (PI) have the primary responsibility for SAE, device-related AE and DevD identification, documentation, grading, and assignment of attribution to the investigational agent/intervention.

10. Test Articles

Maintain proper storage and control of all test articles.

a. Maintain a complete and accurate investigational test article inventory log. Accurately account for all investigational test articles received by the Investigator, kept in inventory, dispensed to subjects, returned by subjects, and returned to the Sponsor.
b. Return test articles as instructed upon completion or termination of the clinical study, or at the Sponsor's request.

11. Study Records

Maintain adequate and accurate records of all clinical study data, which are generally more exact and complete than those kept in ordinary medical practice.

a. Keep study records and source documents until the Sponsor has provided written approval for their destruction.
b. Ensure that data are recorded on source documents and transferred to the appropriate Case Report Forms for each study participant.
c. Adhere to Case Report Form Completion Guidelines provided by the Sponsor.
d. Smith & Nephew requires that all records relating to the conduct of this study be held by the Investigator for a period of at least 2 years following the approval of the test article or removal of the IND. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, custody must be transferred to the Sponsor or to a person who will accept responsibility and is approved by the Sponsor. Study records will not be destroyed without the written approval of the Sponsor.

12. Monitoring and Auditing

Permit monitoring, auditing, and access to all study documents and make them available for inspection and copying by representatives of the Sponsor, the IRB/IEC, regulatory authorities, and other inspectors.

Notify the Sponsor of any written or verbal communication from a regulatory authority or inspector as soon as it occurs and work with the Sponsor to prepare a response to all such communication.

13. HIPAA Authorization

For studies conducted in the US only, obtain written HIPAA authorization (or provide a waiver) for use and disclosure of protected health information (PHI) from each study participant (or legal representative) enrolled in the study using your current authorization form before performing any study-specific procedures on the study participant.

18.13 DECLARATION OF HELSINKI

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP), effective for studies commencing after July 1996.