**Smith & Nephew Wound Management**
**CLINICAL SCIENCES**
**STATISTICAL CONSIDERATIONS - CLINICAL TRIALS**

| ST: | 9 | 7 | 5 | Reference: | CE/052/PIC | Customer Code: | 0 | 5 |
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| **Study Title:** | 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 |

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| **This Issue** | FINAL | 5TH JUNE 2015 |
| **Previous Issues:** | | |

## STATISTICAL CONSIDERATIONS APPROVAL

The signing of this document signifies that the Statistical Considerations have been laid down in full agreement of the author and the reviewing statistician.

5/6/2015
DATE

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# 1. INTRODUCTION

## 1.1 TRIAL OBJECTIVES

The primary objective of this study is to compare PICO against ActiV.A.C.® in terms of wound progression, namely the percentage change in the target ulcer area, over the 12-week treatment period

The secondary objectives of this study are:

- KEY SECONDARY: Compare PICO against ActiV.A.C.® for the percentage change in the target ulcer depth and volume over the 12-week treatment period
- SECONDARY:

  (1) To compare PICO against ActiV.A.C.® in the time (days) to achieve confirmed complete target ulcer closure by either surgical intervention or secondary intention

  (2) To compare PICO against ActiV.A.C.® for the proportion of subjects that achieve confirmed complete target ulcer closure by either surgical intervention or secondary intention

  (3) To compare PICO against ActiV.A.C.® 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 ActiV.A.C.® in terms of:

  - 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

## 1.2 OVERVIEW

This Statistical Analysis Plan (SAP) document describes the statistical considerations, including data analysis methods for Protocol CE/052/PIC. Related documents to this SAP are the Study Protocol, Case Report Form (CRF), and Table Templates (Shells).

The study database(s) includes all of the CRF-based clinical data, central laboratory data and data collected within the interactive web-based response system (IWRS). Sealed Envelope, a contracted vendor, will assign a randomized treatment based on a pre-defined randomization methodology. All subjects commencing screening will be entered into the IWRS system.

# 2. STUDY DESIGN

## 2.1 DESCRIPTION OF TRIAL 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). Subjects will be randomized to one of two treatment groups to receive either PICO single-use NPWT system or ActiV.A.C. ® System, for 12 weeks, or until target ulcer closure (by surgical intervention or secondary intention), whichever occurs first.

The study consists of four periods: a 1-week run-in period (including screening Run-In Visit 1, Run-In Visit 2), a 12-week randomized treatment period (including Study Visit 1 through Study Visit 12), a 1-week end-of-treatment assessment period (including Study Visits 13, 14). Study Visit 14 serves as the end of study visit.

Following a 1-week run-in period, approximately 160 subjects meeting entry criteria will be randomly assigned to one of the two treatment arms in a 1:1 allocation ratio to receive treatment with either PICO single-use NPWT system or ActiV.A.C. ® system for 12 weeks with dressing changes as deemed required in the opinion of the investigator or required in the instructions for use (IFU).

Eligible subjects will receive treatment for 12 weeks (Visits 1 through 12), or until their wound closes or progressing sufficiently to become ready for surgical closure in the opinion of the investigator. Subjects whose wounds have closed, as assessed by the Investigator, prior to the 12th week of treatment (or Visit 12) will stop treatment and return for one further visit (Visit 14) to verify if the target ulcer remains closed for one week following the initial observation of ulcer closure. An ulcer which remains closed at this one week verification assessment is defined as having achieved complete wound closure in this study.

For those subjects who are randomized and who discontinue from the study prior to Visit 13 due to any reasons other than target wound closure, Visit 14 will serve as the early termination (ET) visit.

The size of the target ulcer, pain associated with target ulcer will be assessed for each subject at Run-In Visit 1 (screening). This information, along with the status of

the target ulcer will be assessed at Run-In Visit 2/Study Visit 1 (baseline), and Study Visits 2 – Study Visit 12, Study Visit 13 (no treatment application), and Visit 14 (Confirmation of complete wound closure/End of Study if the ulcer remains open during the 12-week treatment period).

## 2.2 SCHEDULE OF ASSESSMENTS

The complete schedule of assessments for this study is shown in table below.

Visits are allowed to have a window of ±1 day for the Screening Run-In 1/Run-In 2 and Study Visits 2-14 where applicable.

At Screening, eligible subjects will be assessed for baseline ulcer measurements (i.e., area, perimeter, depth and volume) using the ARANZ Silhouette System, duration of the target ulcer, pain associated with target ulcer, details of previous treatment(s) and medical history. After a one-week run-in period, Run-in Visit 2/Study Visit 1, eligible subjects will be randomized to receive PICO or ActiV.A.C. ®. At each of the weekly visits from Visit 1 through Visit 13, the subject's ulcer measurements (i.e., size, perimeter, and depth), ulcer status, and details relating to the treatment application, resource use and secondary applications. Pain associated with the target ulcer during treatment and on treatment application will be assessed. The subject will receive a further treatment application according to the randomisation schedule, where necessary at the clinic, except for Visit 13 at which the subject receives no further treatment. Ulcer size, perimeter, depth and volume will be measured using the ARANZ device. Pain will be assessed using a 100-mm Visual Analog Scale (VAS) and wound status will be assessed using a modified Bates-Jensen wound assessment tool.

At Study Visit 1 and End of treatment, the subject will complete two Health Related Quality of Life survey, namely the EQ-5D and the Cardiff Wound Impact Schedule. At the End of the Study visit (Visit 14), the subject will also complete an Exit Survey.

**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 (CWIF, 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 Principal 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 CWIF and EQ-5D only if the target ulcer is closed or will be surgically closed during the treatment period.
e Subjects to complete CWIF, EQ-5D and VAS assessments only if the target ulcer remained open during the treatment period.

## 2.3 EFFICACY/SAFETY MEASURES AND ENDPOINTS

### 2.3.1 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 at each study visit by the Investigator. The percentage change in target ulcer area over the 12-week treatment period is

then derived using the baseline area and the area recorded at Study Visit 13. 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 $cm^2$. 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.

### 2.3.2 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 over the 12-week treatment period will be derived using the baseline depth and the depth recorded at Study Visit 13. The endpoint will be repeated for ulcer volume.

The remaining secondary endpoints are detailed below:

- 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. Complete wound closure is defined as complete re-epithelialization, without drainage or the need for a dressing, confirmed at one-week post initial ulcer closure.
  When an ulcer closure is initially observed at a weekly treatment visit from Visits 2 to 13, it will be confirmed at the one further study assessment one week later (Visit 14) so that it can be considered as a complete wound closure.

- The time in days to (confirmed) ulcer closure 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 as the number of days between the date of the randomization visit (Study Visit 1) and the date

at which ulcer closure first occurred. For those subjects who drop out or who do not achieve the complete wound closure during the 12-week treatment period, the time to complete wound closure will be considered as censored at the last visit date (censored date) of the treatment period or 84 days (i.e. 12 weeks x 7 days), whichever occurs earlier.

- 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 Cardiff Wound Impact Schedule (CWIS) validated instruments.

  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 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. 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. 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.

The Cardiff Wound Impact Schedule (CWIS) 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

Study subjects will complete both instruments at the Randomization Study Visit 1 and at the End of Treatment period. Scoring/coding of responses, and 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 will be calculated according to the suppliers validated instructions.

### 2.3.3 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 sum of duration of wear for the subject and the number of dressings utilized by the subject.

### 2.3.4 SAFETY ENDPOINTS

Adverse events are recorded at each visit. Vital signs (blood pressure and pulse) are measured at Screening.

Routine laboratory tests are conducted at Screening to confirm eligibility. Laboratory tests are analyzed by a central laboratory and include the following parameters:

**Hematology**: Red Blood Cell (RBC) count, Hemoglobin, Hematocrit, Platelets, White Blood Cell (WBC) total count, and differential (%) including absolute counts (x 109/L)

**Blood Biochemistries**: Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin, Total Protein, Urea, Glucose, and HbA1c

**Additional Chemistries**: Pre-albumin

### 2.3.5 HANDLING OF MISSING, INCOMPLETE, AND REPEAT DATA

The handling of missing data and/or missing planned visits is described in the following section for the primary endpoint and secondary endpoints.

Percentage change in ulcer Area – Primary Endpoint:

The percentage change in target ulcer area over the 12-week treatment period is derived using the baseline area and the area recorded at Study Visit 13. Missing values and/or visits may occur at these visits if data is not collected or a subject discontinues from the treatment due to wound closure or early termination. In cases where the target ulcer area is missing or an ARANZ image cannot be taken due to the ulcer being closed in the opinion of the Investigator, the ulcer area at the Study Visit will be imputed as 0 $cm^2$.

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.

Percentage change in ulcer Depth/Volume – Key Secondary Endpoint:

The methods detailed above for the handling of missing/incomplete data regarding the primary endpoint will also be used for Depth and Volume.

Proportion of subjects with confirmed ulcer closure – Secondary Endpoint:

The subject's ulcer closure status (open or closed) will be assessed by the Investigator at each study visit. Closure is confirmed at one-week post initial ulcer closure. Missing values and/or visits may occur at these visits if data is not collected at the Study Visit, or a subject discontinues from the treatment due to wound closure or early termination. Missing data may also exist if the one-week closure

confirmation visit is not attended. In cases where the ulcer closure status is missing at a Study Visit or the subject is withdrawn from the study, the Last Observation Carried Forward (LOCF) method will be used (with the exception of the confirmatory period).

In addition, two separate sensitivity derivations will be performed to account for missing data:

- Worst case: 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.
- Best case: 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 to achieve complete closure – Secondary Endpoint:

Once a subject achieves complete ulcer closure as defined above, the time to complete ulcer closure will be calculated as the time interval in number of days between the date of randomization (i.e. Study Visit 1) and the date of the initial observation of the wound ulcer closure. For those subjects who drop out or who do not achieve the complete wound closure during the 12-week treatment period, the time to complete wound closure will be considered being censored at the last visit date (censored date) of the treatment period (i.e. from Study Visits 2 to 13) or 84 days (i.e., 7 days x 12 weeks), whichever occurs earlier. There is no missing data for time to achieve complete closure.

Difference between treatments in Health Related Quality of Life (HRQoL) – Secondary Endpoint:

The EQ-5D and CWIS instruments will be completed at Randomisation (Study Visit 1) and End of treatment. Missing data can occur with the questionnaires due to missed questions or the subject being unwilling to answer. Missed visits may also cause missing data. In cases where questions are skipped, the missing responses will be coded as per the instrument guidelines. Separately, in cases where there are missing individual responses (not complete missing questionnaires) contained on the end of treatment questionnaire, these will be coded as the Last Observation Carried Forward (LOCF) from the baseline questionnaire.

Ulcer progression parameters – Exploratory Endpoint:

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. Missing values and/or visits may occur at these visits if data is not collected or a subject discontinues from the treatment due to ulcer closure or early termination.

In cases where the ulcer is recorded as closed in the investigators opinion the following imputations will be made at the corresponding Study Visit to account for the missing values recorded:

- Presence of infection = No
- Presence of clinical signs of infection = No
- Level of Exudate = None/No
- Extent of undermining = None
- Necrotic tissue present = No
- Epithelialization at target ulcer = 100% wound covered, surface intact

Remaining values which are required to be analysed at the end of the 12-week treatment period will utilize the Last Observation Carried Forward (LOCF) method for the last non-missing post-baseline Study Visit.

In cases where dressing wear time cannot be calculated for a single dressing (for example, loss to follow up with no removal assessment recorded), the average wear time for the subject will be calculated for the trial duration up to (and excluding) the dressing with unknown duration of wear.

Safety Endpoints:

Any resultant incomplete or missing data of vital signs or safety parameters will be treated as missing in the statistical analyses involving these parameters.

# 3. STATISTICAL CONSIDERATIONS

## 3.1 DETERMINATION OF SAMPLE SIZE

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%. This was calculated using EAST 6. 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. A recommendation may be made at this point to stop the trial prematurely due to efficacy or futility.

## 3.2 RANDOMIZATION

All eligible subjects will be randomized between PICO and ActiV.A.C.® therapy settings by means of an online randomisation system (Sealed Envelope).
Treatment will be randomized, stratified by wound type and wound size at the conclusion of the screening period (and prior to commencement of the treatment period) 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 $cm^2$)*

- *Large VLU (>12 $cm^2$)*

A blocked randomization will be used for each stratum utilizing a block size of 2 and 4. Due to visible differences between treatments, allocation to treatment will not be blinded.

### 3.3 INTERIM REVIEW

An interim analysis 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. 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). If assumptions relating to normality not hold, the corresponding p-value boundary scale values will be used.

## 4. ANALYSIS PLAN

### 4.1 General

Smith & Nephew Wound Management Global Medical and Clinical Affairs will conduct data management and statistical analysis. Unless otherwise stated, all significance tests will be two-sided tests at the 5% significance level. P-values will be quoted and 95% confidence intervals will be generated where appropriate. All p-values will be rounded to three decimal places, p-values less than 0.001 will be presented as '<0.001' in all tables.

All descriptive statistics will be summarized by treatment (PICO or ActiV.A.C.®) and by target ulcer type (Venous Leg Ulcer or Diabetic Foot Ulcer) and combined ulcer types. All summaries will be repeated separately by site. In addition, all wound progress summaries [primary variable, proportion of patients (and time to) achieve

confirmed closure] for the ActiV.A.C.® treatment arm will be separated by predominant therapy used, either continuous or intermittent therapy, and overall. Modifications to this summary approach, including additional variables of separation, will be defined where necessary in the following sections.

Subjects are able to be re-screened up to a maximum of two times in the case of screen failure. This results in a maximum of three screening periods (Run-In Visit 1:Run-In Visit 2) per subject. In the case of multiple screening periods being conducted, unless otherwise stated, the following summaries should include only the last screening period conducted for a given subject. Unless otherwise defined, baseline is defined as Study Visit 1.

## 4.2 Statistical Methods

Unless otherwise specified, 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.

## 4.3 Derived Data

1. A flag for patient inclusion in the full analysis set. If the patient has received NPWT and has at least one (post-baseline) dressing change assessment then the patient is included in the full analysis set. Otherwise the patient is excluded from the full analysis set.

2. A flag for patient inclusion in the safety population. If the patient has received NPWT, then the patient is included in the safety population. Otherwise the patient is excluded from the safety population.

3. The duration in days between the baseline assessment (Randomization Study Visit 1) and each scheduled Study Visit (2-12) (scheduled every 7 days) and Study Visit 13 or 14.

4. The duration in days between the Screening Run-In Visit 1 and Screening Run-In Visit 2.

5. A flag for whether the Screening Run-In Visit 2 occurred 7 (±1) days after Screening Run-In Visit 1.

6. The duration in days between the baseline assessment (Randomization Study Visit 1) and each scheduled Study Visit (2-12) (scheduled every 7 days) and Study Visit 13/14.

7. A flag for whether study visits occurred weekly after the Randomization Visit as per the protocol. A separate flag should be derived for each study visit.
   E.g. Study Visit 2 should occur at 7 (±1) days after the Randomization Study Visit 1. Study Visit 3 should occur at 14 (±1) days etc.

8. The duration in days between the Study Visits i and j (where i≥1 and j=i+1)

9. Patient age (years) defined as: The date of the baseline assessment – date of birth/365.25

10. Patient body mass index defined as: Weight (kg)/ (Height (cm/100))$^2$

11. Reference wound duration at point of randomisation will be derived as follows:
    Date of Target onset date - Date of Randomization Visit 1

12. The (post-screening) study duration (in days) will be derived as follows:
    Date of Study Completion - Date of Randomization Visit 1

13. The Screening duration (in days) will be derived as follows (separately for screening, re-screen 1 and re-screen 2 where appropriate):
    Date of Run-In Visit 2 - Date of Run-In Visit 1

14. The number of screening periods per subject will be derived as:
    No re-screening periods used = 1
    A single re-screening period used = 2
    Two re-screening periods used = 3

15. The change in target ulcer area during the screening period will be derived as (change in depth and volume will be derived using the same method):

$$Area_{Run-In\,2} - Area_{Run-In\,1}$$

16. The percentage change in target ulcer area during the screening period will be derived as (percentage change in depth and volume will be derived using the same method):

$$\left(\left(\frac{Area_{Run-In\,2} - Area_{Run-In\,1}}{Area_{Run-In\,1}}\right) \times 100\right)$$

17. Target ulcer area is defined as surface area as measured by the ARANZ Silhouette Device at each study visit by the Investigator. For each study visit, the change in target ulcer area will be derived as (change in depth and volume will be derived using the same method):

Change in target ulcer area at Study Visit n = $Area_{SVn} - Area_{SV1}$

18. For each study visit, the percentage change in target ulcer area will be derived as (percentage change in depth and volume will be derived using the same method):

Percentage change in target ulcer area at Study Visit n = $\left(\left(\frac{Area_{SVn} - Area_{SV1}}{Area_{SV1}}\right) \times 100\right)$

For purposes of the primary analysis, the percentage change in target ulcer area will be derived as using LOCF within the 12-week treatment period. The percentage change in depth and volume will be derived using the same method.

19. The time to achieve confirmed ulcer closure in days will be derived as follows:
    - For those subjects that achieve confirmed closure (derived variable 20):
      Date of Study Visit where closure is first recorded – Date of Randomization
    - For those subjects that achieve closure but do not achieve confirmation (derived variable 20):
      Date of Study Visit where closure is first recorded – Date of Randomization
    - For those subjects that do not achieve closure during the 12-week treatment period or withdraw early, the time to achieve confirmed ulcer closure will be defined as either: Date of last study visit attended – Date of Randomization;
      Or 84 days, whichever occurs earlier.

20. Whether confirmed ulcer closure was achieved will be derived as follows:
    - Ulcer Closed/Ready for surgical closure=Yes at last attended Study Visit i, Ulcer Closed=Yes at Follow up assessment (Visit 14). Confirmed Closure = Yes
    - Ulcer Closed/Ready for surgical closure =Yes at last attended Study Visit i, Ulcer Closed=No at Follow up assessment (Visit 14). Confirmed Closure = No
    - Ulcer Closed/Ready for surgical closure =Yes at last attended Study Visit i, Ulcer Closed=missing at Follow up assessment (Visit 14). Confirmed Closure = missing
    - Ulcer Closed/Ready for surgical closure =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.

21. The derivation for whether confirmed ulcer closure was achieved will be repeated to form two further separate variables, with the exceptions below:

    i. 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. All remaining scenarios will be derived as described in the previous derived variable.

    ii. 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. All remaining scenarios will be derived as described in the previous derived variable.

22. The components of the CWIS will be derived as follows at baseline and end of treatment.

    a) <u>Physical symptoms and daily living</u>

    Each individual response will be coded by the following formulae:

Not at all/Not applicable – 5

Seldom/Slightly – 4

Sometimes/Moderately – 3

Frequently/Quite a bit – 2

Always/Very – 1

An overall score for this domain will then be calculated as the sum of the 24 individual values (12 individual values each for experience and stress related measures).

The overall score will then be transformed onto a scale of 0-100 using the following formula:

[(Overall actual score (sum of 24 individual scores) – minimum possible score) / range of possible scores] * 100

If all 24 questions are completed, the minimum value =24 and the range of scores = (120 - 24) = 96

b) Social Life

Each individual response will be coded by the following formulae:

Not at all/Not applicable – 5

Seldom/Slightly – 4

Sometimes/Moderately – 3

Frequently/Quite a bit – 2

Always/Very – 1

An overall score for this domain will then be calculated as the sum of the 14 individual values (7 individual values each for experience and stress related measures).

The overall score will then be transformed onto a scale of 0-100 using the following formula:

[(Overall actual score (sum of 14 individual scores) –minimum possible score) / range of possible scores] * 100

If all 14 questions are completed, the minimum value =14 and the range of scores = (70 - 14) = 56

c) Well-being

Each individual response will be coded by the following formulae:

Strictly disagree – 5

Disagree – 4

Not sure – 3

Agree – 2

Strongly agree – 1

NOTE: 'I am confident that the wound(s) I have will heal' will be coded in reverse (strictly disagree-1, disagree-2, not sure-3, agree-4, strongly agree-5).

An overall score will be calculated as the average of the 7 individual values for the wellbeing domain.

The overall score will then be transformed onto a scale of 0-100 using the following formula:

[(Overall actual score (sum of 7 individual scores) – minimum possible score) / range of possible score] * 100

If all 7 questions are completed, the minimum value =7 and the range of scores = (35 - 7) = 28

23. The change in each of the CWIS scores (Wellbeing, Physical symptoms and daily living, Social life, Overall HRQoL and Patient Satisfaction with overall HRQoL) between baseline and end of treatment period will be derived separately as:

*Score at Baseline (Randomization) – Score at End of Treatment*

24. The responses to the individual EQ-5D-5L domains will be coded as detailed in the references (§6) for the Mobility, Self-care, Usual Activities, Pain/Discomfort and Anxiety/Depression domains. The individual domain responses on a scale of 1-5 will be combined in the previously defined order to form a 5-digit number in the form XXXXX (where X is 1-5) describing the respondent's health state.

25. The change in EQ-5D VAS between baseline and end of treatment period will be derived as:

*Score at Baseline (Randomization) – Score at End of Treatment*

26. The duration of dressing wear (dressing level) for each individual dressing will be derived as follows per assessment:

If no unscheduled visit takes place between consecutive assessments:
Duration of wear = Date of removal visit – Date of application visit – duration of study therapy interruption
If an unscheduled visit takes place between consecutive assessments multiple duration of wear values will be derived:
Duration of wear 1= Date of unscheduled visit – Date of application study visit
Duration of wear 2= Date of removal study visit – Date of unscheduled visit – duration of study therapy interruption
If more than one unscheduled visit occurs between consecutive assessments, further multiple wear times will be derived as above.

27. The average wear time per patient (patient level) will be derived as follows per subject:
    Sum of duration of dressing wear (dressing level) values / Count of duration of dressing wear (dressing level) values

28. The median value for the baseline (Run-In Visit 2/Study Visit 1) target ulcer area will be derived for both the Full Analysis Set and Per Protocol populations by wound type and overall. The median value will also be derived for the depth and volume.

29. Whether or not the reference ulcer is clinically infected at any Study Visit.

30. Whether or not the reference ulcer has signs of infection at any Study Visit.

31. Whether an intervention was required will be derived for each subject:
    If an unscheduled visit is recorded, where the reason for intervention is not given as routine: Intervention = Yes
    If no unscheduled visits are recorded: Intervention = No

32. Whether prescription of an antibiotic was required will be derived for each subject:
    If "have any systemic antibiotics been prescribed" = Yes at any assessment, or any antibiotic medications are recorded on the concomitant medications form, with a start date after randomization: Antibiotic = Yes

If "have any systemic antibiotics been prescribed" = No at all assessments, and no antibiotic medications are recorded on the concomitant medications form: Antibiotic = No

33. Whether an intervention or prescription of an antibiotic was required will be derived for each subject:
    If Intervention derivation (Derived Variable 31) = Yes or Antibiotic derivation (Derived Variable 32) = Yes, then need for intervention or antibiotic= Yes
    If Intervention derivation (Derived Variable 31) = No or Antibiotic derivation (Derived Variable 32) = No, then need for intervention or antibiotic= No

34. All pain assessments (dressing removal, during wear, on initiation of therapy) will be derived as follows:
    In cases where pain = No, the VAS pain value will be coded as 0

35. Level of Exudate (amount) will be coded as follows- In cases where Exudate presence=No, then the level/amount of exudate will be coded as None.

36. The responses to the aspects of the wound assessment tool (BWAT-M); Undermining, Necrotic Tissue Type, Necrotic Tissue Type, Necrotic Tissue Amount, Exudate Type, Exudate Amount, Skin Color Surrounding Wound, Granulation Tissue and Epithelialization will be coded at each study visit as defined in Section 7. The individual coded values will then be summed at each individual study visit to give a total wound status score.

37. The personnel time taken at each Study Visit will be derived as:
    No. of personnel applying the dressing x time taken to apply the NPWT system

38. The total personnel time taken at throughout the study will be the sum of the personnel time at Study Visits per subject.

39. The duration for which compression therapy was interrupted at each Study Visit in hours will be derived as: hours + (daysx24). If no interruption is recorded then the number of hours will be coded as 0.

40. The duration for which study therapy was interrupted at each Study Visit in hours will be derived as: hours + (daysx24). If no interruption is recorded then the number of hours will be coded as 0.

41. The total duration (in hours) for which compression therapy was interrupted per subject will be calculated as the sum of the interrupted duration at each Study Visit.

42. The total duration (in hours) for which study therapy was interrupted per subject will be calculated as the sum of the interrupted duration at each Study Visit.

43. In cases where the ulcer is recorded as closed in the investigators opinion the following imputations will be made if missing values are present:
    - Presence of infection = No
    - Presence of clinical signs of infection = No
    - Level of Exudate = None/No
    - Extent of undermining = None
    - Necrotic tissue present = No
    - Epithelialization at target ulcer = 100% wound covered, surface intact

44. Individual flags for whether each event was a serious adverse event, severe adverse event, investigational device related adverse event, a serious investigational device related adverse event, an unexpected adverse event and a serious unexpected adverse event.

45. Individual flags for whether a patient experiences: a serious adverse event, severe adverse event, investigational device related adverse event, a serious investigational device related adverse event, an unexpected adverse event and a serious unexpected adverse event.

46. The duration of resolved adverse event in days defined as: End date – start date.

47. The duration of adverse events at study completion defined as:
    End date – start date for adverse events that resolved during the study period.
    Date of study completion – start date for adverse events with no end date.

## 4.4 Patient Analysis Sets

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 treatment within the first nine (9) weeks (- 1 day) and have no significant protocol deviations. 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.

The numbers of subjects in each analysis data set will be summarized and listings of patients excluded from each analysis set along with the reasons for exclusion will be provided.

## 4.5 Disposition of Patients

The numbers of subjects that are screened, the number of subjects that enter the study (i.e. are randomized) and the number of subjects that attend Study Visit 2-14 will be summarized.

The screening duration will be summarised for all subjects separately for screening period, re-screening period 1 and re-screening period 2, and overall. The number of screening periods (including any re-screen periods) per subject will also be summarised.

The reasons for study completion and withdrawal will be summarised. The study duration will be summarised by reason for study completion and overall.

Details of the dates that the first subject was screened, first subject randomized and the last patient completed will be provided.

## 4.6 Protocol Deviations

The occurrence of the following examples of protocol deviations and significant protocol deviations, and the number of subjects with a protocol deviation and significant protocol deviation will be summarized:

- Patients that do not meet the inclusion/exclusion criteria but are randomized (the reason for failure of inclusion/exclusion criteria will be summarized)
- Subjects with a PICO duration of dressing wear is >7 days where no wound filler is used
- Subjects with an ActiV.A.C.®, or PICO in combination with a wound filler, with a duration of dressing wear >3 days
- Missed Study Visit

- Patients that receive study treatment with NPWT for greater than 85 days (12 weeks allowing +1 day)
- Patients taking a prohibited concomitant medication
- Patients with a serious device related adverse event who are not withdrawn from study treatment
- Attendance of weekly Study Visit outside ±1 day window
- Failure to complete the Subject Exit survey or Health Related Quality of Life questionnaires (EQ-5D or CWIS) at the required timepoints

## 4.7 Measurement of Treatment Compliance

The number of treatment applications per subject will be summarized. In addition, subject attendance at each Study Visit will be summarized.

## 4.8 Baseline Data

Demographics

Patient demographics including age, gender, height, weight and body mass index (BMI) will be summarised. Race and Ethnicity will also be summarized.

Medical History

Relevant medical history (presence/absence of relevant medical conditions and duration since onset), diabetes status, and type of diabetes will be summarized.

Smoking status and patient mobility will be summarized.

Reference ulcer details

Reference ulcer type including grade of Diabetic Foot Ulcers will be summarised.

The side and location of the reference wound, the duration of the reference wound, how many ulcers are on the target leg, whether the ulcer has ever healed and recurred, and arterial supply measurements (ABI, GTP, TcPO2, and waveform pattern) will be summarized.

Whether the target ulcer has had any previous treatment, if so the products used, including the duration of NPWT, type of compression and type of offloading therapy will be summarized. The dressings applied for the duration of the screening run-in period will be summarized. The intended method of ulcer closure will also be summarized.

Reference ulcer dimensions at Run-In Visit 2 (baseline) including area, perimeter, depth and volume will be summarised. In addition the change and percentage change in reference ulcer dimensions during the Screening/Run-In period will be summarized.

Homogeneity of treatment groups

Individual two-sample t-tests will be used to test for a difference in the means of the following baseline characteristics between treatment sequence groups separately for each wound type (VLU/DFU) and overall: patient age, BMI, baseline wound area, wound duration and level of wound pain recorded during Screening Run-In Visit 1. If the assumptions of the t-test are violated, Wilcoxon rank sum test will be used instead with median Hodges-Lehmann estimates of the differences reported.

Individual Cochran-Mantel-Haenszal tests will be used to test for a difference in the following baseline characteristics between treatment sequence groups separately for each wound type (VLU/DFU) and overall: level of exudate.

## 4.9 Primary Variable

The primary objective of the study is to compare PICO against ActiV.A.C.® in terms of the percentage change in the target ulcer area, over the 12-week treatment period.

Primary Analysis

An initial linear regression model will contain covariates for treatment, center, wound type, baseline (defined as Run-In Visit 2/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.

Non-inferiority will be concluded if the upper bound of the 95.4% confidence interval for the parameter estimate relating to treatment covariate (coded as ActiV.A.C.® – 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 non-parametric 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 up to a maximum of 10,000 replicates.
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 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.

Secondary Analysis

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.

The baseline area, final area, absolute change in area and percentage change in ulcer area over the 12-week treatment period will be summarized separated by treatment, centre, wound type and area used for stratification purposes (large/small) and baseline area (<median/>=median). Further summaries will be produced separated by the covariates used in the final model. The ulcer area, change in area and percentage change in area will be summarized by Study Visit (2-12) and

treatment, centre, wound type and area used for stratification purposes (large/small). Summaries will utilize the Per Protocol Population and will be repeated for the Full Analysis Set.

## 4.10 Secondary Variables

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 detailed in the primary analysis.

The baseline depth, final depth, absolute change in depth and percentage change in ulcer depth over the 12-week treatment period will be summarized separated by treatment, centre, wound type and baseline depth (<median/>=median). Further summaries will be produced separated by the covariates used in the final model. The ulcer depth, change in depth and percentage change in depth will be summarized by Study Visit (2-12) and treatment, centre, wound type and baseline depth (<median/>=median). Summaries will utilize the Per Protocol Population and will be repeated for the Full Analysis Set. The summaries detailed for ulcer depth will be repeated for the target ulcer volume.

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 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 (Hat Matrix Diagonal, Pearson residuals, Deviance residuals, DFBETAs, C and CBAR, DIFDEV and DIFCHISQ). For each model, overdispersion will be tested for by examining the deviance and pearson statistic divided by their degrees of freedom. If these are not approximately equal to 1 then an adjusted analysis may be used for overdispersion using quasi-likelihood methods.

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 terms of the 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) Worst case: 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) Best Case: 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.

Whether confirmed closure was achieved will be summarised by Study Visit (Note: initial observation of closure will be summarized not the visit where closure was confirmed). The wound status (open/closed/re-opened) will be summarized for the Study Visit 14 assessment.

Whether the wound is closed (not confirmed), if so the method (surgical or secondary intention), and method of surgical closure if appropriate, and the treatment to be received post-closure will be summarised by Study Visit

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 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.

In each case, the assumption of proportional hazards will be verified using plots of the log cumulative hazard against log time for each treatment and each of the other factors and by assessing the treatment x time interactions. If the model assumptions of a proportional hazards do not hold such that the log cumulative hazard plots against log time are not parallel, the time interactions are significant ($p<0.05$) or if $N<40$ and an expected frequency of at least one cell is $< 5$ then a Log Rank Test may be applied. 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. All analyses relating to Quality of Life assessments will be performed using the Full Analysis Set.

**Cardiff Wound Impact Schedule**

The parameters for each of the domains of the CWIS questionnaire (Wellbeing, Physical symptoms and daily living, Social life) in addition to Overall HRQoL and Patient Satisfaction with overall HRQoL at baseline and end of treatment will be summarized using frequency distributions which will detail the number and percentage of subjects which fall into each category. The change in the CWIS score for each of the domains between baseline and end of treatment will be summarized.

A two sample t-test will be used to test for a difference in the mean change in CWIS score between treatments for each of the domains separately. 95% confidence intervals will also be presented. If the assumptions of the t-test are violated, the Wilcoxon rank sum test will be used instead with Hodges-Lehmann estimates of the median difference and 95% confidence interval reported.

As a sensitivity analysis, the above analysis will be repeated with any missing values coded using LOCF.

**EQ-5D**

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.

The change in EQ VAS and derived TTO index between the Randomization Visit and the End of Treatment period will also be summarized. A two sample t-test will be used to test for a difference in the mean change in EQ VAS between treatments. 95% confidence intervals will also be presented. If the assumptions of the t-test are violated, the Wilcoxon rank sum test will be used instead with Hodges-Lehmann estimates of the median difference and 95% confidence interval reported. This analysis will be repeated separately for the change in TTO index.

## 4.11 Exploratory Variables

**Presence of Infection and 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 using the Full Analysis Set, the corresponding 95% confidence intervals will also be presented.

The presence of infection and clinical signs of infection will be summarized by regular Study Visit, at treatment discontinuation and, where appropriate at the one-week confirmation visit. Whether the reference wound is clinically infected at any post baseline assessment will also be summarised.

In addition, the summaries will be separated by reference wound filler used at baseline (gauze, foam or none).

Whether the reference wound has signs of clinical infection at any post baseline assessment and whether the reference wound has signs of clinical infection at treatment discontinuation will be cross tabulated against whether the reference wound has signs of clinical infection at baseline separately for each treatment.

**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 antibiotics or additional interventions, between treatments using the Full Analysis Set. The corresponding 95% confidence intervals will also be presented. Individually, Fishers Exact tests will be used to test for a difference in the percentage of subjects requiring the administration of antibiotics and additional interventions separately, between treatments.

The need for administration of antibiotics and additional interventions (and either intervention), and type of intervention will be summarized at per subject by treatment and wound type.

**Dressing wear time**

A linear regression model will be fitted to the average wear time per subject. Treatment, center, wound type, baseline ulcer area, baseline exudate level and baseline mobility 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.

The standardised residuals will be assessed for normality (histograms, quantile-quantile plots), homoscedacity (plots against regressors) and no large outliers (magnitude, covariance ratio, DFBETAS). Should these assumptions not hold or if N<20 then non-parametric bootstrapping may be applied to generate 95% confidence intervals of the model estimates. If these differ widely from those of the linear regression model then the bootstrapping estimates will be used these will be used.

The average wear time per subject (at a subject level) will be summarized by treatment, wound type, and the remaining covariates detailed in the previous paragraph. The duration of dressing wear (at a dressing level) will also be summarized by treatment, center, wound type, level of mobility at baseline, 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 response questions to the exit survey will be summarized by treatment, center, wound type and baseline level of mobility.
A Cochran-Mantel-Haenszel will be used to test for a difference between treatments in individual responses to the Exit Survey for: Overall satisfaction, Opinion of using the device on another wound in future, comfortable to wear, activity level change, and the use of the NPWT device was disruptive to my sleep.

**Pain on removal of dressing, at initiation of therapy and during wear**

The level of pain on initiation of therapy will be summarized by Study Visit and treatment, separately for each wound type and overall.
The level of pain on initiation of therapy will also be summarized for the ActiV.A.C.® treatment arm overall Study Visits by whether intermittent or continuous therapy is applied, and by pressure range applied (for intermittent – the high therapy pressure value will be used), and compression rate, at the current Study Visit.

The level of pain during wear, and on removal, will be summarized by Study Visit and treatment, separately for each wound type and overall.
The level of pain during wear, and on removal, will also be summarized for the ActiV.A.C.® treatment arm overall Study Visits by whether intermittent or continuous therapy is applied, and by pressure range applied (for intermittent – the high therapy pressure value will be used), and compression rate, at the current Study Visit.

In addition, the level of pain recorded on removal of the screening dressings at Run-In Visit 2 will be summarized by wound type.

**Wound Assessment**

The presence of necrotic tissue, extent of undermining, the necrotic tissue type and amount, granulation tissue type, epithelialisation tissue type, skin condition surrounding target ulcer, and condition of target ulcer peri-wound will be summarized by Study Visit, at treatment discontinuation and at one-week closure confirmation.

The level (amount) of exudate and the type of exudate will be summarized by Study Visit, at treatment discontinuation and at one-week closure confirmation.

The total wound status score will be summarized by Study Visit, at treatment discontinuation and at one-week closure confirmation.

## 4.12 Other Data Summaries

Intended method of closure

The intended method of ulcer closure recorded at Study Visit 1 will be cross-tabulated against the actual method of closure recorded for those ulcers that achieve closure, with the remaining ulcers coded as not-closed.

This summary will be repeated including only those wounds that achieved confirmed closure; the remaining ulcer will be coded as not-confirmed closure.

Ulcer Debridement

Whether the target ulcer was debrided, and the type of debridement used, will be summarized by Study Visit and overall. Separately, whether the target ulcer was debrided, and the type of debridement used, will be summarized at Run-In Visit 2.

Interruption of study therapy

Whether the study therapy was interrupted between study visits, and if so, how long for (in hours), will be summarized overall Study Visits by treatment.

Additionally, the total time per subject for which the study therapy was interrupted between study visits will be summarized by treatment.

Interruption of compression therapy

Whether the compression therapy was interrupted between study visits, and if so, how long for (in hours), will be summarized overall Study Visits by treatment.

Additionally, the total time per subject for which the compression therapy was interrupted between study visits will be summarized by treatment.

Resource Use

The dressing applied, kit size used, whether a filler was used, the filler used, will be summarised at each Study Visit and overall. Whether the subject is using any compression therapy or pressure relieving/offloading therapy, and the type of therapy/equipment used will be summarized.

The device therapy mode and pressure setting (continuous), high/low therapy set points and time on/off cycle times (intermittent), and adjustable compression rate will be summarized for ActiV.A.C.® subjects only.

The personnel time taken (in minutes) to apply the NPWT system will be summarized overall Study Visits by treatment, and separated by intermittent/continuous, and by whether any filler dressing was used.
In addition, the total personnel time taken (in minutes) to apply the NPWT system for each subject will be summarized by treatment. A two sample t-test will be used to test for a difference in the mean total time taken (in minutes) to apply the NPWT system between treatments. 95% confidence intervals will also be presented. If the assumptions of the t-test are violated, the Wilcoxon rank sum test will be used instead with Hodges-Lehmann estimates of the median difference and 95% confidence interval reported.

The number of personnel (and type of personnel) applying the device will be summarized overall Study Visits by treatment, and separated by intermittent/continuous, and by whether any filler dressing was used.

Continuing Dressing Usage

Whether any dressings were applied at Study Visit 14 will be summarized by treatment and by whether the ulcer is open / closed at Study Visit 14.

## 4.13 Safety

All safety analyses and summaries will be conducted using the Safety Population.

Extent of Exposure

The duration of treatment with NPWT will be summarized by treatment.

Adverse Events

Adverse events will be coded and grouped by system organ class using the Dictionary for Medical Drug Regulatory Activities (MedDRA). Adverse event summaries will separately be presented for the screening period, treatment period

(Study Visit 1 – Visit 14) and overall. Unless otherwise stated, all safety summaries will be presented by treatment and wound type (DFU or VLU) and overall.

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 values, including the numbers of subjects that are below (abnormal), within and above (abnormal) the normal ranges, upon entry to the screening period will be summarized.

Hematology: Red Blood Cell (RBC) count, Hemoglobin, Hematocrit, Platelets, White Blood Cell (WBC) total count, and differential (%) including absolute counts (x 109/L)

Blood Biochemistries: Sodium, Potassium, Calcium, Creatinine, Total Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin, Total Protein, Urea, Glucose, and HbA1c

Additional Chemistries: Pre-albumin

Vital Signs, Physical Findings

The vital signs recorded upon entry to the screening period (including Resting Heart Rate, Respiratory Rate, Blood pressure (systolic and diastolic) and Blood pressure measurement location will be summarized.

Concomitant Medications

The number and percent of subjects that take pre-randomization concomitant medications relevant to the target ulcer will be summarized. The number and percent of subjects who take post-randomization concomitant medications relevant to the target ulcer will be summarized separately for new and existing concomitant medications.

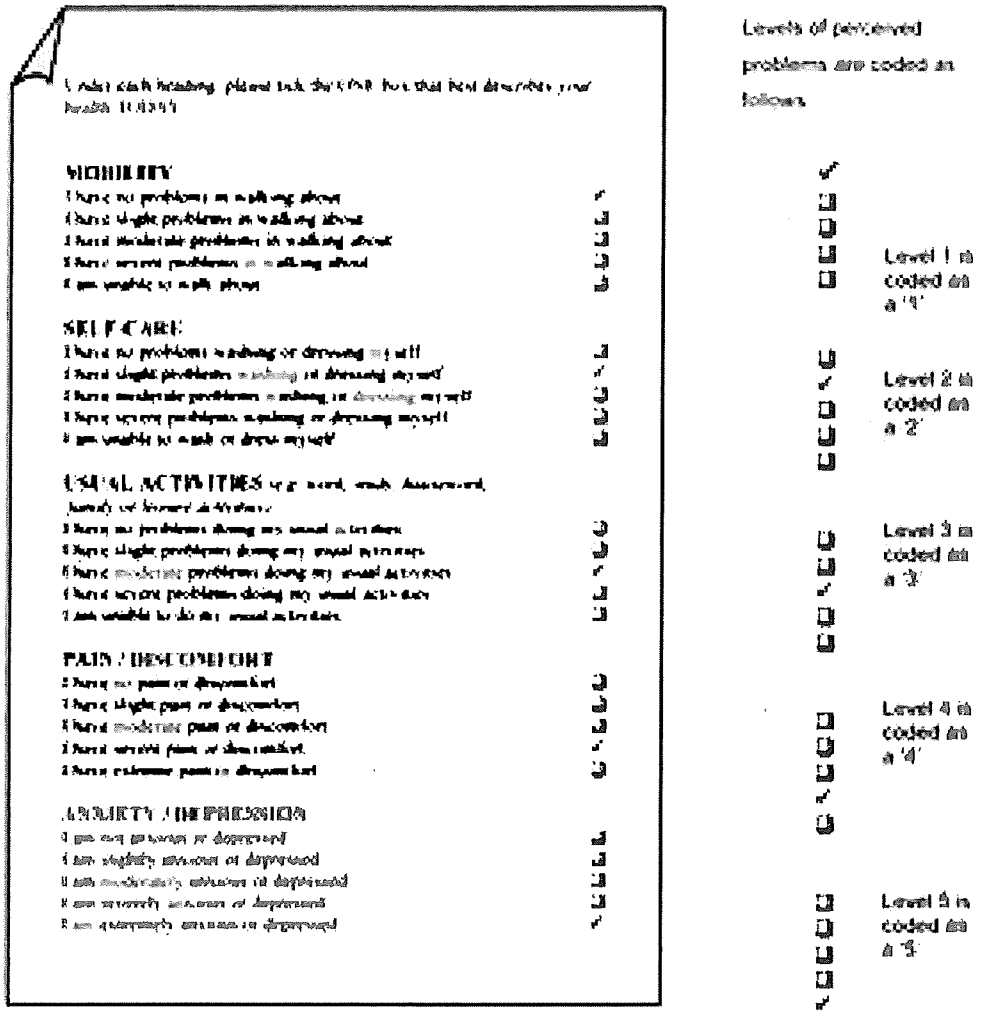
# 5 References

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

Mark D. Rothmann, 2011. *Design and Analysis of Non-Inferiority Trials (Chapman & Hall/CRC Biostatistics Series).* 1 Edition. Chapman and Hall/CRC.

# 6 How to Score EQ-5D-5L

The EQ-5D-5L descriptive system should be scored, for example, as follows:




This example identifies the health state '12345'.

**NB:** There should be only ONE response for each dimension.

**NB: Missing values** can be coded as '9'.

**NB: Ambiguous values** (e.g. 3 boxes are ticked for a single dimension) should be treated as missing values.

EuroQol Research Foundation. 2015. EuroQol - How to use EQ-5D. [ONLINE] Available at: http://www.euroqol.org/about-eq-5d/how-to-use-eq-5d.html. [Accessed 27 March 15].

# 7 How to Score Wound Assessment scoring tool (BWAT-M)

| Item | Assessment |
|---|---|
| **1. Undermining** | 1 = None present<br>2 = Undermining < 2 cm in any area<br>3 = Undermining 2-4 cm involving < 50% wound margins<br>4 = Undermining 2-4 cm involving > 50% wound margins<br>5 = Undermining > 4 cm or Tunneling in any area |
| **2. Necrotic Tissue Type** | 1 = None visible<br>2 = White/grey non-viable tissue &/or non-adherent yellow slough<br>3 = Loosely adherent yellow slough<br>4 = Adherent, soft, black eschar<br>5 = Firmly adherent, hard, black eschar |
| **3. Necrotic Tissue Amount** | 1 = None visible<br>2 = < 25% of wound bed covered<br>3 = 25% to 50% of wound covered<br>4 = > 50% and < 75% of wound covered<br>5 = 75% to 100% of wound covered |
| **4. Exudate Type** | 1 = None<br>2 = Bloody<br>3 = Serosanguinous: thin, watery, pale red/pink<br>4 = Serous: thin, watery, clear<br>5 = Purulent: thin or thick, opaque, tan/yellow, with or without odor |
| **5. Exudate Amount** | 1 = None, dry wound<br>2 = Scant, wound moist but no observable exudate<br>3 = Small<br>4 = Moderate<br>5 = Large |
| **6. Skin Color Surrounding Wound** | 1 = Pink or normal for ethnic group<br>2 = Bright red &/or blanches to touch<br>3 = White or grey pallor or hypopigmented<br>4 = Dark red or purple &/or non-blanchable<br>5 = Black or hyperpigmented |
| **7. Granulation Tissue** | 1 = Skin intact or partial thickness wound<br>2 = Bright, beefy red; 75% to 100% of wound filled &/or tissue overgrowth<br>3 = Bright, beefy red; < 75% & > 25% of wound filled<br>4 = Pink, &/or dull, dusky red &/or fills < 25% of wound<br>5 = No granulation tissue present |
| **8. Epithelialization** | 1 = 100% wound covered, surface intact<br>2 = 75% to < 100% wound covered &/or epithelial tissue extends to > 0.5 cm into wound bed<br>3 = 50% to < 75% wound covered &/or epithelial tissue extends to < 0.5 cm into wound bed<br>4 = 25% to < 50% wound covered<br>5 = < 25% wound covered |