STATISTICAL ANALYSIS PLAN

Sponsor Name
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STUDY TITLE

A Prospective Study of Quality of Life in Patients with Chronic Leg Wound(s) Treated with Prontosan® Wound Irrigation Solution and Prontosan® Wound Gel

Protocol No: OPM-G-H-1506

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
HbA1c	Glycated Hemoglobin
ICF	Informed Consent Form
IFU	Instructions for Use
MedDRA	Medical Dictionary for Regulatory Activities
PHMB	Polyaminopropyl biguanide (polyhexanide)
PT	Preferred Term
QoL	Quality of life
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TIME	Tissue, Infection/Inflammation, Moisture, Edge

1. INTRODUCTION

Chronic leg wounds are those that do not progress through the normal healing process in a timely manner. In the United States alone, these wounds are estimated to affect between 2.4 to 4.5 million patients.[1] Chronic wounds are typically classified as vascular ulcers (venous and arterial ulcers), diabetic ulcers, and pressure ulcers. As these wounds last on average 12 to 13 months and recur in up to 60% to 70% of patients, they can lead not only to a loss of function and a decreased quality of life, but also to an increase in morbidity. Primarily a condition of the elderly, chronic wounds are becoming more prevalent as populations age in developed countries and are associated with high treatment costs, estimated at 2% to 3% of the healthcare budgets in these countries.[2]

The physiological process of wound healing progresses through 4 main phases: hemostasis, inflammation, proliferation, and remodeling.[3] Immediately after an injury, vasoconstriction and blood clotting occurs, preventing blood loss and providing a provisional matrix for cell migration. Platelets secrete growth factors, and cytokines attract endothelial cells, fibroblasts, and immune cells. The inflammation stage usually lasts up to 7 days, during which time phagocytic cells are at work: neutrophils release reactive oxygen species and proteases that prevent bacterial contamination and cleanse the wound of cellular debris, and monocytes differentiate into tissue macrophages that remove bacteria and nonviable tissue and release growth factors and cytokines. As blood vessels are repaired and immune cells undergo apoptosis, the inflammation phase winds down and the proliferation phase begins. During the proliferation phase, tissue granulation, angiogenesis, and epithelialization occur. During the remodelling phase, which begins after the wound has closed and may last 1 to 2 years or longer, the provisional matrix is remodelled into organized collagen bundles.[3]

Chronic wounds often stall in the inflammation phase. Although they may differ in etiology, chronic wounds usually share some common features: elevated levels of proinflammatory cytokines, proteases, reactive oxygen species, and senescent cells; persistent infection; and a deficiency of stem cells and/or dysfunctional stem cells. Repeated tissue injury induces platelet-derived factors to stimulate the constant influx of immune cells; thus, the proinflammatory cytokine cascade becomes amplified and persists for a prolonged period, leading to elevated levels of proteases. Eventually, protease levels exceed the levels of their inhibitors, leading to the destruction of the extracellular matrix and the degradation of growth factors and their receptors. The destruction of the matrix not only prevents a progression to the proliferative phase, but also attracts more inflammatory cells, amplifying the inflammation cycle. Similarly, elevated levels of reactive oxygen species also damage the extracellular matrix, which stimulates proteases and inflammatory cytokines. This amplified inflammation cycle, together with the deficiency of functional stem cells, results in a failure to achieve complete re-epithelialization in tissue repair.[3, 4]

In caring for chronic wounds, the concurrent management of both the underlying systemic problem (e.g., diabetes, peripheral arterial disease) and the wound bed preparation encourages the proper environment in which autolytic tissue repair can take place. The basic tenets of wound bed preparation have been described by the TIME acronym: Tissue assessment and management, Infection/Inflammation management, Moisture imbalance management, and Edge of wound observation and management.[3] For tissue management, repetitive and maintenance debridement and wound cleaning are recognized as essential throughout the healing period. As almost all chronic wounds are thought to contain biofilms, topical antiseptics are commonly used to control bioburden in wounds. Excessive or insufficient wound exudate can be addressed with a wide range of dressings to regulate moisture balance, to protect peri-wound skin, and to optimize healing. At the edge of the wound, therapies such as negative pressure wound therapy may be used to help improve epithelial advancement and wound closure.[5]

Topically applied agents available for debridement, cleaning, and moistening acute and chronic wounds include such solutions as sterile saline, honey, povidone-iodine, cadexomer iodine, hypochlorous acid, a "super-oxidized" solution (sodium chloride/ sodium hypochlorite/ hypochlorous acid solution), collagenase, and polyhexamethylene biguanide [PHMB] (Prontosan® Wound Irrigation Solution and Prontosan® Wound Gel).[3, 6]

2. STUDY OBJECTIVES

The primary objective of this study is to assess the overall change in the QoL after 4 weeks of treatment with Prontosan solution and Prontosan gel in patients with chronic leg wound(s). This will be determined by calculating the change from baseline in the global score of the Wound-QoL questionnaire.

The secondary objective is to assess the changes in the Body, Psyche, and Everyday Life subscores of the Wound-QoL questionnaire after 4 weeks of treatment with Prontosan solution and Prontosan gel.

The exploratory objective is to assess the change in the appearance and size of the wound(s) by direct evaluation and photographic measurements after 4 weeks of treatment with Prontosan solution and Prontosan gel.

3. STUDY DESIGN

This is a prospective, open-label, multi-site, single-arm study in patients with chronic leg wound(s). The investigator or designee will apply Prontosan solution and Prontosan gel to the wound(s) at clinical visits Week 1, Week 2, Week 5. Patients will apply Prontosan solution and Prontosan gel themselves (or have them applied by a caregiver) at home (Week 3 and Week 4). The study contains Screening period (Week 0), 4 weeks of treatment period (Week 1 – Week 5), and safety follow-up.

The schedule of assessments to be performed throughout the study is given in the protocol.

4. ANALYSIS POPULATIONS

4.1 Enrolled Population

The Enrolled Population includes all patients who signed the informed consent form at the Screening visit and met the inclusion/exclusion criteria while participating at the Week 1 visit.

4.2 Evaluable Population

The Evaluable Population includes all patients who receive at least 2 weeks of study treatment and complete the Week 3 Wound-QoL questionnaire.

The analyses of primary endpoint, secondary endpoints, and exploratory endpoints will be done in the evaluable population.

4.3 Safety Population

The safety Population (SAF) includes all patients with at least one study treatment administration.

All safety assessment analysis will be done in the safety population. In addition, the primary and secondary endpoint analysis will be repeated using the safety population.

Safety assessments include vital signs, physical examinations, adverse event (AE) and ADE (adverse device effect) review, and clinical laboratory tests.

4.4 Completer Population

The Completer Population includes all patients who complete the 4-week treatment period (Week 5).

The analyses of the primary, secondary and exploratory endpoints will be repeated using this population.

5. STATISTICAL METHODOLOGY

5.1 Statistical and Analytical Issues

5.1.1 Statistical Methods

All data will be summarized, and where necessary, data will also be listed. For continuous variables, data will be summarized with the number of patients (n), mean, SD (standard deviation), median, minimum, and maximum. For categorical variables, data will be tabulated with the number and proportion of patients for each category.

For the primary analysis of the change from baseline to Week 5 in the global score of the Wound-QoL questionnaire, a paired t-test will be performed using PROC MEAN procedure in

SAS version 9.4. This inferential statistical analyses comparing global score change will be interpreted in an exploratory sense only at an alpha level of 5% for statistical significance.

5.1.2 Handling of Dropouts and Missing Data

Patients who prematurely withdraw from the study for any reason should complete the early discontinuation visit requirements. If the early discontinuation visit is not done, the reason(s) will be recorded in the eCRF. Patients who withdraw or are withdrawn before completion of the Week 2 assessments and the Week 3 Wound-QoL questionnaire will be replaced to ensure that at least 52 patients will complete the study.

The questionnaire consists of 17 statements of impairments. The patient assesses and documents the degree to which the impairments affected him/her within the previous 7 days by ticking checkboxes using a Likert scale from 0 to 4: 0=not at all, 1=a little, 2=moderately, 3=quite a lot, 4=very much. The global score is an average of the completed questionnaire items, which can be calculated if at least 13 out of 17 items are completed.

If more than 1 box is checked within an item, or if a patient has checked between 2 checkboxes, the item is treated as missing. Missing items are not averaged in the global score. A global score can be computed only if at least 75% of the items have been answered and are not treated as discarded or as missing (at least 13 of the 17 items are valid), and a subscore (Body, Psyche, and Everyday Life) can be computed only if no more than 1 item of the subscale is missing.

5.1.3 Determination of Sample Size

A sample size of 52 patients will have 80% power to detect a change from baseline to Week 5 of at least 0.35 points in the Wound-QoL global score (e.g., a baseline mean Wound-QoL global score of 3.53 and a follow-up mean Wound-QoL global score of 3.18), assuming an estimated SD of differences of 0.88, using a paired t-test with a 0.050 two-sided significance level. Patients who withdraw or are withdrawn before completion of the Week 2 assessments and the Week 3 Wound-QoL questionnaire will be replaced to ensure that at least 52 patients will complete the study.

5.1.4 Time Windows

In this post-marketing study, data will be collected from each patient at screening, baseline (Week 1), Week 2, Week 3, Week 4 and Week 5 (final visit). The Week 1 baseline visit will be scheduled at <= 1 week after screening visit with a window of +/- 1 day. For the visits Week 2 up to Week 5, a window of ±1 day will be allowed for patient data collection.

All patients are to adhere to the visit schedule as specified in the flowchart (Table 1). If any visit or assessment has to be rescheduled and deviates from the given time window, this visit or assessment, will be handled as out of window. Subsequent visits should follow the original visit date schedule. Out of window and unscheduled assessments will be listed, but not used for descriptive analysis and calculation of primary and secondary endpoints.

5.1.5 Patient Disposition

Patient disposition will be summarized as indicated below using the Enrolled Analysis Population. The disposition categories will be summarized by number and percentage using the number of enrolled patients as a percentage denominator:

- Enrolled patients
- Safety population
- Evaluable population
- Completer population
-

Patient disposition information will be listed. In addition, patients who were discontinued from the treatment or who did not complete the treatment will also be presented in this listing, including early termination reason. A subject is considered a statistical completer (Evaluable population) if he/she receives at least 2 weeks of study treatment and completes the Week 3 Wound-QoL questionnaire.

5.1.6 Protocol Deviations

Protocol deviations will be listed as well as summarized and grouped into different categories such as

- Violation of inclusion/ exclusion criteria
- Time schedule deviations
- Non-compliance based on the investigator or designee's compliance records in eCRF.
- Missing essential data such as incomplete wound-QoL questionnaire data
- Patient not discontinued as per protocol of study (in case of infection or treatment with prohibited medication)
- Other non-compliance

Multiple deviations can occur in the same patient and thus a patient can be counted in more than 1 deviation category.

Patient listings of protocol deviations will include reasons for non-compliance and will be sorted by site.

5.1.7 Demographics and Baseline Wound History Characteristics

Patients demographics are age [years], weight [kg], height [cm], body mass index (BMI) [kg/m2], sex, race, and ethnicity.

All data as recorded in the eCRF are used for the analyses of patient demographics.

Regarding age, the age at the time of the baseline visit is recorded in the eCRF.

Categorical patient baseline wound history variables are:

1) Wound type
    - Venous Ulcer
    - Arterial Ulcer
    - Diabetic Ulcer
    - Burn (1st or 2nd Degree)
    - Cellulitis
    - Soft Tissue Necrosis
    - Neuropathic Ulcer
    - Traumatic Ulcer
    - Collagen Vascular
    - Infectious

2) Wound description
    - Partial Thickness Wound
    - Full Thickness Wound

3) Wound location
    - Left leg
    - Right leg
    - Left foot
    - Right foot

4) Wound location on the leg or foot
    - Medial
    - Lateral
    - Anterior
    - Posterior

5) Past complications
    - Infection
    - Recurrent Hospitalizations
    - Others

Patient demographic and baseline background information will be summarized in tables for the safety, evaluable and completer population.

Descriptive statistics (sample size, mean, median, standard deviation [SD], minimum [Min] and maximum [Max]) will be presented for continuous variables: age, body mass index [BMI], height, weight, wound age, and wound surface area. Frequency counts and percentages will be tabulated for categorical variables: gender, ethnicity, race, and baseline target wound history and characteristics categories. As each subject may have 2 chronic wounds, which will be treated and assessed, we will need to distinguish between the 2 wounds for the purpose of descriptive analysis (i.e. wound #1 and wound #2). Baseline target wound characteristics will also be listed in order to include a description of other past complications. Only 1 wound must meet all of the inclusion/exclusion criteria.

5.1.8 Treatment Exposure

Administration of study treatment in the clinic will be performed by the Investigator or designee, ensuring compliance with the individual patient's regimen.

Exposure in terms of administered Prontosan solution and Prontosan gel will be listed and summarized descriptively by week for the safety population.

5.1.9 Prior and Concomitant Medications and Therapies

Prior medications are defined as those taken by or administered to the patient before screening and up to the first study treatment. Concomitant medications are defined as those taken by or administered to the patient after the first study treatment.

Medications will not be coded and only listings of reported terms will be presented.

In case of incomplete stop date a medication or therapy will be considered as prior if this can be concluded without any doubt. All other cases will be considered concomitant medication or therapy administered during the 4-week treatment period.

The medication indication, the regimen, start and stop date will be displayed. The listings will differentiate between prior and concomitant medications in the safety population by the order of the medication/therapy start date.

5.1.10 Medical Histories

The assessment of an illness being previous or concomitant is entered directly in the eCRF by the investigator.

Prior illnesses that the patient has experienced prior to signing the Informed Consent Form (ICF); this is the patient's previous illnesses. New illnesses present after the ICF is signed and up to the time of first treatment (Week 1) are to be regarded as concomitant illnesses.

Illnesses are not coded by Medical Dictionary for Regulatory Activities (MedDRA). All medical history data will be presented in a patient data listing.

Medical history will be displayed separately for prior and concomitant illnesses in the safety population.

5.2 Statistical Analysis

In this phase IV study, statistical analysis will focus on clinical outcome assessments. The clinical outcome assessments include patient-reported Wound-QoL questionnaire, and investigator-reported wound(s) size and assessments.

5.2.1 Primary Analysis

The primary endpoint is defined as

- Change from baseline to Week 5 in the global score of the Wound-QoL questionnaire.

The primary endpoint will be analysed by the following primary analysis in the evaluable and completer populations.

Let μ be defined as expected value of change from baseline to Week 5 in the global score of the Wound-QoL questionnaire.

The null hypothesis to be tested is that μ is equal to 0, i.e., no score change from baseline. The alternative hypothesis is that μ is different from 0. i.e.:

$H0: \mu = 0$ vs. $H1: \mu \neq 0$.

The null hypotheses will be tested using a paired t-test statistic. The t-test is conducted using Proc MEANS procedure in SAS version 9.4. The null hypothesis will be rejected at a two-tailed significance level of 0.05.

In addition, descriptive statistics (n, mean, SD, median, min, max) will be provided in the evaluable population for the primary endpoint. Associated the 95% CI and p-value will be presented for the change from baseline to Week 5 in the global score of the Wound-QoL questionnaire.

The primary endpoint analysis will also be repeated using the safety and completer populations.

5.2.2 Secondary Variable(s)

The secondary endpoints are:

- Change from baseline to Week 5 in the Body subscore of the Wound-QoL questionnaire
- Change from baseline to Week 5 in the Psyche subscore of the Wound-QoL questionnaire
- Change from baseline to Week 5 in the Everyday Life subscore of the Wound-QoL questionnaire

All secondary endpoints will be analysed using the summary statistics primarily in the evaluable population. This analyses will be repeated using the safety and completer populations. For continuous variables, data will be summarized with the number of patients (n), mean, SD, median, minimum, and maximum. Wound-QoL questionnaire subscores are defined in the Appendix 1.

5.2.3 Exploratory Variable

The exploratory endpoint is:

- Change from baseline to Week 5 in the appearance and size of the target wound(s)

As each subject may have 2 chronic wounds, which will be treated and assessed, we will need to distinguish between the 2 wounds for the purpose of descriptive analysis (i.e. wound #1 and wound #2). The appearance of wound(s) includes categorical variables: surrounding erythema (yes, no), swelling categories, odor categories, and colour categories. The size of wound(s) is continuous variable measured in cm^2.

The continuous exploratory endpoint variable will be analysed by the summary statistics for each of the two wounds. Data will be summarized with the number of patients (n), mean, SD, median, minimum, and maximum. For categorical variables, frequency counts and percentages will be used to summarize the results. The number of non-missing values will be used as denominator in percentage calculations. To analyse change from the baseline for categorical

variables, the shift table from baseline to week 5 will be displayed for surrounding erythrema and swelling for each of the two wounds.

This analysis will be conducted in the evaluable population and repeated using the completer population.

5.2.4 Subgroup Analysis

To analyse change from baseline for categorical variables, the shift table from baseline to Week 5 will be displayed for each of the 2 wounds and any additional subgroup analyses will be specified depending on the data observed. The global score and change from baseline in Wound-QoL questionnaire will be summarized by subgroup category and week in the evaluable population.

5.2.5 Other Variables

There will be no hypothesis test for other variables, thus all of them will be conducted based on descriptive statistics. The other variables to be analysed are:

- Weekly global score and its change from baseline in Wound-QoL questionnaire
- Weekly Body subscore, Psyche subscore, and Everyday Life subscore and their change from baseline in Wound-QoL questionnaire
- Weekly appearance and size of wound(s)
- Weekly proportion of patients with no score of 3 or 4 given in each individual item in Wound-QoL questionnaire

The continuous variables global scores and size of wound(s) will be analysed by the summary statistics by week (weeks 1, 2, 3, 4, 5) with the number of patients (n), mean, SD, median, minimum, and maximum.

For categorical variable appearance of wound(s), frequency counts and percentages will be used to summarize the results by week. The number of non-missing values will be used as denominator in percentage calculations.

The first two analyses above will be conducted in the evaluable, safety and completer populations whereas the last two analyses will be conducted in the evaluable and completer populations.

5.2.6 Adverse Events

Any adverse event that occurs at or after first study treatment administration and up to the end of the study treatment is considered as treatment emergent adverse event (TEAE).

An adverse event starting before the first study treatment and worsened in intensity between the first administration of study treatment and the end of the study treatment will also qualify as a treatment emergent adverse event (TEAE).

Pre-existing diseases or conditions occurring before screening visit are considered to be medical history and should be recorded as TEAEs only if they worsen (untoward change in intensity, frequency, or quality) after the first study treatment.

For adverse events where the intensity changes over time, the maximum intensity observed during the whole duration of the adverse event will be documented and captured in the database. If the adverse event stopped and reoccurred with a different or the same intensity, it will be entered as new adverse event in the eCRF.

All AEs with start date after screening visit but before first study treatment administration and that do not worsen after the first study treatment administration, and all AEs with start date after the date of end study treatment will be regarded as non-TEAE. This study will not display non-TEAEs in the tables or listings.

In case of incomplete start/stop date, an AE will be considered as non-TEAE if this can be concluded without any doubt. All other cases will be considered TEAE occurred during the 4-week treatment period. The non-TEAEs will not be included in the AE analysis.

Related TEAEs are entered “yes” as documented in the eCRF.

The following overview table will be generated.

Summary of the number of patients with

- At least 1 TEAE
- At least 1 serious TEAE
- At least 1 related TEAE
- At least 1 TEAE leading to discontinuation from the treatment (i.e. TEAE with “ Action take with Prontosan due to AE”: “stopped both”)
- A TEAE with a fatal outcome

Unless stated otherwise, the following TEAE summaries will be presented:

The number and percentage of patients with serious TEAEs will be summarized by System Organ Class (SOC) and PT (sorted alphabetically).

The percentage denominator will be the number of patients in the safety population.

Adverse Device Effects (ADEs) are considered as AEs that are related to the study device. The possible anticipated ADEs with Prontosan solution or Prontosan gel include AEs: burning sensation, itching, and rash. The suspected unexpected serious adverse reactions (SUSARs) are

serious ADEs that have not previously been documented in the protocol or other safety information.

The number and percentage of patients with ADEs will be summarized by SOC and PT (sorted alphabetically) for each

- ADE
- Serious ADE

Only serious AEs and ADEs will be coded according to MedDRA, version 20.0 or higher. All AEs will be listed. All AE analysis will be conducted in the safety population.

5.2.7 Analysis of Other Assessments

5.2.7.1 Vital Signs

Vital signs will be measured at Week 0 screening visit and Week 5/or early discontinuation visit. Vital signs comprise systolic and diastolic blood pressure, pulse rate and temperature.

Vital signs parameters will be listed for the safety population.

5.2.7.2 Laboratory Parameters

Laboratory parameters are assessed at screening visit and Week 5/or early discontinuation visit. Only clinically significant laboratory parameters will be recorded. All available laboratory data will be listed for the safety population. This data will also be summarized using the safety population.

5.2.7.3 Physical Examination

A complete physical examination (head, ears, eyes, nose, throat, heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at the screening visit. A brief physical examination will be performed at the Week 5 visit (end of treatment or early discontinuation).

Physical examination data in terms of whether the examination was performed or not including the reason will be listed for the safety population.

5.2.8 Interim Analysis

No interim analysis is planned in the study.

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8. APPENDICES

Appendix 1: Wound-QoL Questionnaire

The Wound-QoL questionnaire (shown below) measures the health-related QoL of patients with chronic wounds.[7,8]

Data Analysis Instructions [9]

If more than one box is ticked within an item or if a patient has ticked between two checkboxes, the item is treated as missing.

Answers to each item are coded with numbers (0='not at all' to 4='very much').

A Wound-QoL global score on overall disease-specific quality of life is computed by averaging all items. A global score can only be computed if at least 75% of the items have been answered (i.e., at least 13 in 17 items are valid).

In addition, subscales of the Wound-QoL can be calculated representing different dimensions of disease-specific quality of life by averaging the respective items. A subscale can only be computed if no more than 1 item of the subscale is missing. The items are assigned to subscales as follows:

1. Subscale 'Body': Items #1 to #5
2. Subscale 'Psyche': Items #6 to #10
3. Subscale 'Everyday life': Items #11 to #16

Item #17 does not belong to either of the subscales.

The following questions are designed to find out how your chronic wound(s) affect(s) your quality of life.

Please check one box per line!

	In the last seven days ...	**not at all**	**a little**	**moderately**	**quite a lot**	**very much**
1	...my wound hurt	O	O	O	O	O
2	...my wound had a bad smell	O	O	O	O	O
3	...the discharge from the wound has upset me	O	O	O	O	O
4	...the wound has affected my sleep	O	O	O	O	O
5	...the treatment of the wound has been a burden to me	O	O	O	O	O
6	...the wound has made me unhappy	O	O	O	O	O
7	...I have felt frustrated because the wound is taking so long to heal	O	O	O	O	O
8	...I have worried about my wound	O	O	O	O	O
9	...I have been afraid of the wound getting worse or of getting new wounds	O	O	O	O	O
10	...I have been afraid of hitting the wound against something	O	O	O	O	O
11	...I have had trouble moving around because of the wound	O	O	O	O	O
12	...climbing stairs has been difficult because of the wound	O	O	O	O	O
13	...I have had trouble with everyday activities because of the wound	O	O	O	O	O
14	...the wound has limited my recreational activities	O	O	O	O	O
15	...the wound has forced me to limit my contact with other people	O	O	O	O	O
16	...I have felt dependent on help from others because of the wound	O	O	O	O	O
17	...the wound has been a financial burden to me	O	O	O	O	O

Appendix 2: Wound Measurement with the Clock Method

Wounds are to be measured using the clock method with the standard, single-use, disposable rulers provided by the Sponsor. With this technique, you will draw an imaginary box around the wound at the longest length and the greatest width of the wound, using the body orientation as an imaginary clock (12:00 is at the head, 6:00 is at the feet). Do not slant the ruler to accommodate the greatest measurement, and remember that sometimes length is smaller than width. You will measure the length and width, in centimeters (cm), of the imaginary box. To measure a wound on the feet, use the heels as 12:00 and toes as 6:00.[10]

To measure the greatest length of the wound (regardless of shape), use the following steps:

1. Picture the face of the clock lying over the wound bed with 12:00 pointing toward the patient's head and 6:00 toward the patient's feet.
2. Locate the part of the wound that is closest to 12:00 and draw a line (in your mind) from that point straight across the body.
3. Locate the part of the wound that is closest to 6:00 and draw another line (in your mind) from that point straight across the body.
    - Now you have 2 parallel lines framing the top and bottom of the wound.
4. Place a standard, single-use, disposable ruler between these 2 parallel lines to measure the greatest length in cm.

To measure the greatest width of the wound, use the following steps:

5. Locate the part of the wound that is closest to 9:00 and draw a line (in your mind) at that point straight up and down (head to foot).
6. Locate the part of the wound that is closest to 3:00 and draw another line (in your mind) at that point straight up and down.
    - Now you have 2 parallel lines framing the left and right sides of the wound, thus completing the imaginary box around the wound.
7. Place a standard, single-use, disposable ruler between these 2 parallel lines to measure the greatest width in cm.
8. Remember to document all measurements in cm.

At this point, you have the maximum length (instructions 1 to 4) and the maximum width (instructions 5 to 7) of the wound. You can now calculate the surface area of the wound (length x width) in cm^2. To qualify for this study, the wound must be between 10 cm^2 and 16 cm^2, inclusive.