Sponsor Name and Address:	T.J. Smith and Nephew Limited 101 Hessle Road, Hull HU3 2BN, England
Investigational and Comparator Product:	ALLEVYN Gentle Border wound dressing No comparator
Protocol Authors:	Hilary Watkins, Clinical Research Analyst Michelle Foster, Senior Biostatistician Kareen Chu, Clinical Study Manager

1. SIGNATURES

1.1 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

This page will be returned to T.J. Smith and Nephew Limited and a copy will be retained at the investigational site.

I have read the attached protocol entitled "A Prospective, Multi-center, Post-Market Clinical Follow-Up Study to Evaluate the Safety and Effectiveness of ALLEVYN Gentle Border," version 3.0, dated 21 JUN 2019, and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in Section 27.1 of the protocol,

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

Name, Address, Professional Position	**Signature**	**Date Signed** (DD/MMM/YYYY)

1.2 SPONSOR APPROVAL

	Job title	DocuSign Stamp
Head of Global Clinical Operations	Sr Director, Global Clinical Operations	DocuSigned by: Omar Merhi Signer Name: Omar Merhi Signing Reason: I approve this document Signing Time: 25-Jun-2019 | 17:07 BST 077916DA813C42D38DFA82D77A0E07F2
Head of Global Clinical Strategy	VP, Global Clinical Strategy	DocuSigned by: Beate Hanson Signer Name: Beate Hanson Signing Reason: I approve this document Signing Time: 27-Jun-2019 | 11:36 BST A491AB16277146CA9C8B8366F1B6BEA5
Head of Global Biostatistics	Director of Biostatistics	DocuSigned by: Alan Rossington Signer Name: Alan Rossington Signing Reason: I approve this document Signing Time: 26-Jun-2019 | 10:15 BST 556E7DBFCA8A4287A7EE3EE9B5B3ABFD
Medical Affairs Representative	Medical Director	DocuSigned by: Signer Name: Justin Templeton Signing Reason: I approve this document Signing Time: 25-Jun-2019 | 17:54 BST AA2E1C3040C348A39FB3C66B8DE9730A

2. SYNOPSIS

Title of Study:	A Prospective, Multi-center, Post-Market Clinical Follow-Up Study to Evaluate the Safety and Effectiveness of ALLEVYN Gentle Border
Study Design:	• Prospective • Multi-center • Single-arm
Study Type:	Observational Study
Study Product:	ALLEVYN Gentle border is a triple layer foam dressing consisting of a highly absorbent hydrocellular foam pad held between a perforated wound contact layer (WCL) which is coated with a soft silicone gel adhesive and a highly permeable outer top film.
Comparison Group:	No comparison groups.
Study Purpose:	PMCF study to assess clinical performance and safety of ALLEVYN Gentle Border with new wound contact layer to support performance claims.
Primary Objective:	To demonstrate clinical performance of ALLEVYN Gentle Border as measured by reduction in the size of the wound area (cm^2) over 4 week treatment period in patients with chronic and acute; full-thickness, partial thickness or shallow granulating, exuding wounds including pressure ulcers, leg ulcers, diabetic foot ulcers and dehisced surgical wounds.
Secondary Objective:	To generate safety and performance related data of ALLEVYN Gentle Border in patients with chronic and acute wounds.
Other Objective:	None
Statistical Rationale:	It is assumed that the actual reduction in the mean wound area from baseline to 28 days is $3cm^2$ with a standard deviation of $5cm^2$. Assuming this data holds true it can be calculated that 26 subjects would provide 83% power to show a statistically significant reduction in the mean wound area from baseline to 28 days. Accounting for the protocol modifications outlined in Section 21, it is recommended to increase the total patient recruitment target to 35 subjects, providing 93% power. Allowing for a 15% lost to follow up rate, 40 subjects will be recruited into this study.

Sample Size:	40 subjects, with a minimum of 10 subjects in each group of Acute Wounds and Chronic Wounds.
Number of Study Sites:	Up to 8 study sites
Targeted Global Regions:	Up to 3 countries in Europe
Inclusion Criteria:	1. Signed written informed consent. 2. 18 years of age or older. 3. Willing and able to make all required study visits. 4. Able to follow instructions and deemed capable of completing the CWIS questionnaire, Patient Assessment Scale and Pain Scale. 5. Presence of a moderately to highly exuding wound of at least 3cm^2 in size. 6. Presence of a **chronic wound of at least 6 weeks duration** at the point of enrollment; full-thickness, partial thickness or shallow granulating wounds. Chronic wounds include: ○ pressure ulcers or ○ leg ulcers or ○ diabetic foot ulcers. **or** Presence of an **acute wound** at the point of enrolment; full-thickness, partial thickness or shallow granulating wounds. Acute wounds include: ○ dehisced surgical or ○ traumatic wounds. 7. The patient has a wound size which can be treated with the available sizes and shapes of ALLEVYN Gentle Border. Cutting of the dressing is allowed, if needed. ALLEVYN Gentle Border can be cut and an aseptic technique should be used with cutting the dressing. Ensure any exposed foam areas are covered with an appropriate film dressing taking care not to cover the entire dressing.

Exclusion Criteria:	1. Subjects with confirmed or suspected clinically infected reference wound. 2. Reference wound undergoing treatment with compression therapy. 3. Contraindications or hypersensitivity to the use of the ALLEVYN Gentle Border. 4. Participation in the treatment period of another clinical trial within 30 days of Visit 1 or planned participation overlapping with this study. 5. Subjects with skin features (e.g. tattoos, skin color, pre-existing scarring) which, in the opinion of the Investigator, could interfere with the study assessments. 6. Subjects who have participated previously in this clinical trial. 7. Subjects with a history of poor compliance with medical treatment. 8. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study
Study Duration:	Total Study Duration: 26 months Enrolment Period: 13 months Treatment Duration: 4 week Follow-up (5 study visits)
Primary endpoint:	The absolute reduction in wound area from baseline to end of study visit.
Secondary endpoints:	• Absolute reduction in area from baseline to days 7(+/-3), 14 (+/-3), 21 (+/-3). • Absolute reduction in depth and volume from baseline to visits 2, 3, 4 and end of study visit. • Percentage reduction in area, depth and volume from baseline visit to visits 2, 3, 4 and end of study visit. • Exudate management (fluid handling ability including leakage and percentage strikethrough) • Exudate type, amount and viscosity • Odour control – during wear and during dressing change • Dressing change frequency • Condition of surrounding skin • Signs of clinical infection • Healing of reference wound status • Dressing wear time • Dressing retention, presence of bunching up and percentage dressing lift. • Comfort during wear • Showerproof qualities

	• Pain on application, during treatment and on dressing removal <u>Patient Reported Outcome (PRO):</u> • To assess the change from baseline in subject reported outcomes using the Cardiff Wound Impact Schedule (CWIS)
Other exploratory endpoint:	None
Safety Data	Adverse Events and Device Deficiencies data will be collected, such as AEs, SAEs, ADEs, SADEs, USADEs

STUDY SCHEDULE

Table 1: Study Visits and Assessments

Schedule of Events	Key Visits					Other Visits	
	Visit 1 (Baseline) **Day 0**	**Visit 2** **Day 7 (+/-3)**	**Visit 3** **Day 14 (+/-3)**	**Visit 4** **Day 21 (+/-3)**	**End of Study Visit 5** **Day 28 (+/-3)**	**Routine Dressing Changes**	**Treatment Discontinuation** *(before end of study)*
Informed Consent	√						
Demographics/ Medical History	√						
Verify Inclusion/ Exclusion Criteria	√						
Allocate Study ID Number	√						
Concomitant Medication	√	√	√	√	√	√	√
CWIS Patient Questionnaire	√	√	√	√	√		√
Patient Pain Scale	√	√	√	√	√	√	
Patient Assessment		√	√	√	√	√	
Wound Assessment	√	√	√	√	√	√	√
Photograph Dressing in situ Before Removal		√	√	√	√	√	√
Dressing Change		√	√	√		√	
Photograph Wound Before Dressing Application	√	√	√	√	√	√	√
Dressing Performance	√	√	√	√	√	√	

Schedule of Events	Key Visits					Other Visits	
	Visit 1 (Baseline) Day 0	Visit 2 Day 7 (+/-3)	Visit 3 Day 14 (+/-3)	Visit 4 Day 21 (+/-3)	End of Study Visit 5 Day 28 (+/-3)	Routine Dressing Changes	Treatment Discontinuation *(before end of study)*
Adverse Event (AE) Assessment	√	√	√	√	√	√	√
Record Device Deficiencies (DD)	√	√	√	√	√	√	√
End of Study /Exit Form					√		√

3. CONTENTS

3.1 TABLE OF CONTENTS

3.2 TABLE OF TABLES

3.3 TABLE OF FIGURES

3.4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
AGB	Allevyn Gentle Border
BWAT	Bates-Jensen Wound Assessment Tool
CE	Conformité Européene
cm	Centimeter
CRF	Case Report Form(s)
CRO	Contract Research Organization
CV	Curriculum Vitae
CWIS	Cardiff Wound Impact Schedule
DD	Device Deficiency(ies)
DFU	Diabetic Foot Ulcer
EC	Ethics Committee
EPUAP	European Pressure Ulcer Advisory Panel
FU	Follow-Up
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IFU	Instructions for Use
ISF	Investigator Site File
ITT	Intention to Treat population
LTFU	Lost to Follow Up
LU	Leg Ulcer
MedDRA	Medical Dictionary for Regulatory Activities
MVP	Moisture Vapour Permeability

Abbreviation	Definition
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
PI	Principal Investigator
PMA	Pre-Market Authorization
PP	Per-protocol Population
Reference Wound	Identified Study Wound
S&N	T.J. Smith and Nephew Limited, England
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety Population
SAP	Statistical Analysis Plan
TÜV	Technischer Überwachungsverein/ Technical Inspection Association
USADE	Unanticipated Serious Adverse Device Effect(s)
WCL	Wound Contact Layer

4. INTRODUCTION

Chronic wounds, independent from their origin or body location, significantly impact patients' quality of life. These chronic wounds fail to heal and remain stuck in an inflammatory phase. In developed countries, the incidence of chronic wounds has increased in recent years (9), possibly due to an aging population with an abundance of concurrent illnesses such as diabetes, hypertension, obesity, and peripheral vascular disease.

Closure of complex wounds, including chronic wounds, post-surgical wounds, and trauma wounds is often achieved through secondary intention. Although these wound types have different etiologies and underlying pathophysiology, their treatment follows a similar course. Wound closure by secondary intention can be supported by a wide range of wound dressings designed specifically for this purpose. An ideal dressing must provide the following at a minimum:

- a barrier to exogenous contamination and infection
- adequate management of wound exudate
- maintenance of a moist wound healing environment

Failure of a dressing to deliver these fundamental features will negatively impact the ability of a complex wound to heal and may allow the wound to deteriorate. Failure to prevent contamination may allow a wound to become infected. Inability to manage moderate to high exudate volume may lead to maceration of the peri-wound skin, which can lead to further wound breakdown if untreated. At the same time, a dressing should not allow a wound to dry out; the dressing should maintain a moist wound healing environment. The consequences of wound deterioration vary, but can result in protracted wound healing or may cause an otherwise preventable hospital episode for surgical management or closure.

The present study will be the second clinical trial to evaluate the actual use of ALLEVYN Gentle Border (AGB) in clinical practice. In this study, the performance of a new Wound Contact Layer (WCL) will be assessed. The reason for this change was to create a more consistent size in the perforation of the WCL. The new layer is non-adherent to the wound, minimizes stripping of epidermal cells and minimizes the disruption of the healing tissue. In this study, 40 subjects with

acute wounds and chronic wounds older than 6 weeks will be enrolled to assess the performance of AGB with the new Wound Contact Layer (WCL) by the reduction of wound area up to 4 weeks. A summary of known and potential risks and benefits to humans of the test article can be found in the Package Insert and Instructions for Use (IFU).

4.1 LITERATURE SUMMARY

The data provided in the literature suggest that the dressing meets clinician's needs based on dressing wear time, exudate management, wound pain and trauma on dressing removal (2). No wound infections have been identified within the adverse event (AE) profile for ALLEVYN Gentle Border either from PMS or manufacturer sponsored clinical studies (10).

In addition, several clinical studies utilising AGB have been identified demonstrating evidence of the safety and performance of AGB in wound management. A previous comparative clinical study evaluating the use of AGB compared to a competitor dressing demonstrated the safe and effective use in 21 patients with chronic and acute wounds. No major safety issues were highlighted with either dressing and clinicians were satisfied with exudate handling in all AGB dressing changes. (10). A study by Grothier et al. (2009) showed that AGB was rated highly by the investigating clinicians, with an 87% level of acceptance for the range of clinical indications treated. Satisfaction with the dressing's exudate management was reported in 86% of dressing changes. Another case series, including 153 patients, demonstrated that the AGB dressing was effective in improving wound outcomes, in particular reducing wound area, depth and level of exudate in routine clinical practice. Significant reduction in wound area and depth by the final assessment was observed ($p<0.001$; Hurd et al, 2009). Both of these studies, alongside many others (including comparative studies), have demonstrated the safe and effective use of ALLEVYN Gentle Border in wound management (10).

4.2 STUDY PURPOSE

The purpose of this study is to assess the clinical performance and the safety of ALLEVYN Gentle Border with new wound contact layer (WCL).

4.3 SAFETY CONSIDERATIONS

Precautions for the use of AGB, as specified in the current Instructions for Use (IFU), are:

- Care should be taken when using the dressing under medical devices near the nose and mouth, where moisture can build up and affect adherence, leading to dressing movement.
- The use of ALLEVYN Gentle Border, as part of a program of prophylaxis against the development of a pressure ulcer, does not preclude the need to continue to develop and follow a comprehensive pressure ulcer prevention protocol (e.g. regular repositioning, appropriate support surfaces, skin care and frequent skin assessments).
- Due to the gentle adhesive used, do not use this dressing to secure other medical devices to the patient.
- If reddening of the skin or signs of sensitization appear, discontinue use.
- Cutting the dressing will compromise the bacteria barrier and showerproof properties of the dressing.
- Do not immerse the dressing in water.
- Do not use with oxidizing agents such as hypochlorite solutions (e.g. EUSOL) or hydrogen peroxide as these can reduce the absorbency of the dressing.
- Single use only, if used on more than one patient cross contamination or infection may occur.
- Once opened, do not retain unused dressings for application at a later date.
- If used on infected wounds, the infection should be managed as per local clinical protocol.

Risks associated with the use of AGB within the present study will be mitigated as follows:

Study personnel will be trained in the correct use of AGB prior to applying the dressing to the wounds of study subjects.

- Study personnel will be trained on the study protocol.

Study personnel will be directed to carefully follow the inclusion and exclusion criteria for participation in the study when assessing the subject eligibility.

- Study personnel will be directed to read and follow the IFU.

4.3.1 Benefits

ALLEVYN Gentle Border is a silicone gel adhesive hydrocellular foam dressing that provides optimal moist wound healing environment to promote the healing of moderately and highly exuding wounds.

The silicone adhesive layer is gentle, even to fragile skin, and makes it easy to apply, reposition and remove. The dressing has an absorbent foam pad. A breathable top film helps prevent bacterial contamination and is showerproof however the dressing should not be immersed in water.

4.3.2 Other Precautions

This will be the second study with ALLEVYN Gentle Border and its new wound contact layer (WCL) to evaluate the use in clinical practice. There is currently no direct clinical evidence concerning the safety of ALLEVYN Gentle Border with the new wound contact layer. There are no other precautions than listed in section 4.3.

5. OBJECTIVE(S)

The aim of this multi-centre post-market clinical follow-up study is to gather clinical, health economic and safety data on the use of ALLEVYN Gentle Border with new wound contact layer (WCL) in the treatment of chronic wounds in the frame of post-market surveillance for this medical device.

5.1 PRIMARY OBJECTIVE

To demonstrate clinical performance of ALLEVYN Gentle Border as measured by reduction in the size of the wound area (cm^2) over a 4 week treatment period in patients with chronic and acute; full-thickness, partial thickness or shallow granulating, exuding wounds including pressure ulcers, leg ulcers, diabetic foot ulcers and dehisced surgical wounds.

5.2 SECONDARY OBJECTIVE(S)

To generate safety and performance related data of ALLEVYN Gentle Border in patients with chronic and acute wounds.

5.3 CLAIMS

This will be the second study with the new wound contact layer (WCL) to evaluate the entire performance of ALLEVYN Gentle Border in clinical practice. Clinical performance and safety data on AGB will support to extend the current evidence for ALLEVYN Gentle Border.

6. INVESTIGATIONAL PRODUCT

ALLEVYN Gentle Border dressings are composite dressings, which are comprised of three layers as shown in Figure 1. The foam thickness of the middle layer for ALLEVYN Gentle Border is 4 mm thick.

1 A pink, high MVP, polyurethane adhesive pattern spread film, makes up the top layer. This layer is a dynamic breathable top film, allowing for faster fluid removal and aids in the prevention of fluid and bacterial strikethrough

2 A 4-6mm white polyurethane foam absorbent layer (non-patient contacting) makes up the middle layer.

3 A perforated, wound contact layer coated with a silicone adhesive is used in the bottom layer, which allows for the dressing to be easily applied and removed without losing its adhesive properties.

Figure 1: Composite structure of all ALLEVYN Gentle Border Dressings

Finished products are fitted with a release handle on the lower wound contact layer, which protects the adhesive during storage and transport, and which is removed prior to application of the device. The individual dressings are then packaged into 4-sided sealed, peelable pouches before cartoning. The final devices are sterilised by ethylene oxide sterilisation.

6.1 IDENTIFICATION

6.1.1 Investigational Product

ALLEVYN Gentle Border dressings are intended for external use only. They will be applied to the skin, over a wound, at a variety of anatomical sites.

ALLEVYN Gentle Border dressings have been designed in different sizes and shapes.

- ALLEVYN Gentle Border Square
- ALLEVYN Gentle Border Rectangle
- ALLEVYN Gentle Border Multisite

- ALLEVYN Gentle Border Sacrum
- ALLEVYN Gentle Border Heel

The regular shaped ALLEVYN Gentle Border dressing can be left in place for up to seven days, depending on the condition of the wound and the surrounding skin or until exudate is visible and approaches to within 0.5cm of the edge of the dressing pad, whichever is sooner.

Intended Use

ALLEVYN Gentle Border Dressings are indicated for the use in:

- Wound management of chronic and acute; full-thickness, partial thickness or shallow granulating, exuding wounds such as:
  - Pressure ulcers
  - Leg Ulcers
  - Diabetic Foot Ulcers
  - First & Second Degree Burns
  - Donor Sites
  - Fungating ulcers
  - Surgical Wounds
  - Skin Tears
- Pressure ulcer prevention on intact skin, including pressure ulcers caused by medical devices, as part of a pressure ulcer prevention protocol.

Can be used in conjunction with INTRASITE Gel for necrotic or sloughy wounds.

Manufacturer and available sizes

ALLEVYN Gentle Border is manufactured by Smith & Nephew Medical Limited, 101 Hessle Road, Hull, HU32 BN, England.

Sizes and shapes used in this study

The study centers will be provided with ALLEVYN Gentle Border dressings based on the center specific needs. Figure 2 and table 2 show the different sizes and shapes available in the ALLEVYN Gentle Border range.

Figure 2: ALLEVYN Gentle Border Shapes

Table 2: ALLEVYN Gentle Border Size and Ordering Information

S&N code	Dressing size	Carton
66800269	7.5cm x 7.5cm	10
66800270	10cm x 10cm	10
66800900	10cm x 20cm	10
66800264	10cm x 25cm	10
66800265	10cm x 30cm	10
66800272	12.5cm x 12.5cm	10
66800506 (Heel)	23cm x 23.2cm	5
66800959 (Multisite)	17.1cm x 17.9cm	10
66800897 (Sacrum)	16.8cm x 17.1cm	6

AGB is designed to be worn for up to seven days. Subjects will have their dressings changed according to individual clinical need. The total duration of treatment with AGB will also depend on factors such as wound healing, topical wound treatments, or suitability of continued treatment with AGB. If the wound does not heal, the maximum study treatment period will be 4 weeks. In these

4 treatment weeks the dressing will be changed at minimum every week (each 7th day). Depending on the healing process, the number of AGB dressings used by each subject will differ.

6.1.2 Comparator Treatment

There is no comparator treatment in this study.

6.1.3 Ancillary Product

INTRASITE GEL WILL BE PROVIDED ON REQUEST FOR NECROTIC OR SLOUGHY WOUNDS.

6.1.4 Medical Personnel Training

Study centre personnel with responsibilities for the medical care of subjects and/or application of ALLEVYN Gentle Border will be trained by the Monitor or Study Manager on the use and application of AGB prior to enrolling subjects into the study. The training of the investigator will only occur following completion of the clinical trial agreement. Study training of involved medical personnel will involve a presentation on the correct application and use of AGB, including frequency of dressing change.

6.1.5 Application of ALLEVYN Gentle Border

Application of the product will follow the directions from the product IFU.

1. Cleanse the wound in accordance with normal procedures.

2. Select the appropriate dressing size.

3. Prepare and clean the skin surrounding the wound area by removing excess moisture. Any excess hair should be clipped to ensure close approximation to the wound.

4. Start to remove the protector material from the dressing and anchor the adhesive side of the dressing to the skin. (Image A)

5. Smooth the dressing over the wound removing the remaining protector material and ensure that the dressing is adhered all around the wound. (Image B)

6. ALLEVYN Gentle Border can be cut and an aseptic technique should be used with cutting the dressing. Ensure any exposed foam areas are covered with an appropriate film dressing taking care not to cover the entire dressing.

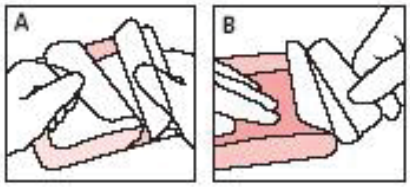


Figure 3: AGB Application Instruction

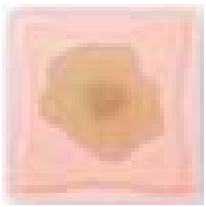
6.1.6 Dressing Change

The investigator will be instructed to follow directions given in the product IFU when changing the study device.

During the early stages of wound management, ALLEVYN Gentle Border dressings should be inspected frequently. Dressings can be left in place for up to 7 days depending on the condition of the wound and the surrounding skin or until exudate is visible and approaches to within 0.5cm of the edge of the dressing pad, whichever is sooner.

No need to change

No need to change



Exudate within 0.5cm of the edge of the pad requires changing

Figure 4: Stages before dressing change

6.2 PACKAGING AND LABELING

6.2.1 Labeling of Investigational Product

ALLEVYN Gentle Border is a marketed product. However, Smith & Nephew will supply each site with ALLEVYN Gentle Border for use during the study. All test articles will be supplied in standard commercial packaging, clearly showing the batch number and expiry date. A label with the following information will be affixed to the AGB packaging without obscuring any regulatory text:

- T.J. Smith and Nephew Limited, England
- Study Number
- Store in a dry place below 25° C
- Keep away from sunlight
- For Investigational Use Only

6.2.2 Storage of ALLEVYN Gentle Border

ALLEVYN Gentle Border should be stored in a dry place below 25°C, and away from sunlight.

6.3 PRODUCT ACCOUNTABILITY PROCEDURES

The Sponsor will keep a record of all AGB dressings supplied to each site. Confirmation of receipt by the Investigator will also be retained. Overall accountability for the accuracy of the used devices is the responsibility of the Investigator or designated individual. All cartons will be clearly identified

per the labeling in Section 6.2.1. The Study Monitor will ensure that the procedures and records are in place to monitor the appropriate use of all test articles.

In addition, any ancillary products (INTRASITE) supplied to the site by the Sponsor will require also a confirmation of receipt by the Investigator and an overall accountability.

Used dressings will be appropriately destroyed per local requirements for clinical waste by the site staff without verification by the study monitor.

7. SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 SUBJECT POPULATION

Forty adult subjects with moderate to highly exuding wounds that require a dressing will be recruited. Only subjects with acute wounds or chronic wounds which are present > 6 weeks will be enrolled. Chronic wounds will include pressure ulcers, leg ulcers, diabetic foot ulcers. Acute wounds will include dehisced surgical or traumatic wounds. In order to ensure a balanced distribution on chronic and acute indications, at least 10 subjects with chronic wounds and at least 10 subjects with acute wounds will be enrolled.

7.2 INCLUSION CRITERIA

Subjects will be considered qualified for enrollment if they meet the following criteria:

1. Signed written informed consent.
2. 18 years of age or older.
3. Willing and able to make all required study visits.
4. Able to follow instructions and deemed capable of completing the CWIS questionnaire, Patient Assessment Scale and Pain Scale.
5. Presence of a moderately to highly exuding wound of at least 3cm^2 in size.
6. Presence of a **chronic wound of at least 6 weeks duration** at the point of enrollment; full-thickness, partial thickness or shallow granulating wounds.
7. Chronic wounds include:

- pressure ulcers or
- leg ulcers or
- diabetic foot ulcers.

or

Presence of **an acute wound** at the point of enrolment; full-thickness, partial thickness or shallow granulating wounds.

8. Acute wounds include:
   - dehisced surgical or
   - traumatic wounds.
9. The patient has a wound size which can be treated with the available sizes and shapes of ALLEVYN Gentle Border. Cutting of the dressing is allowed, if needed. ALLEVYN Gentle Border can be cut and an aseptic technique should be used with cutting the dressing. Ensure any exposed foam areas are covered with an appropriate film dressing taking care not to cover the entire dressing.

7.3 EXCLUSION CRITERIA

Any one (1) of the following criteria will disqualify a potential subject from participation in the study:

1. Subjects with confirmed or suspected clinically infected reference wound.
2. Reference wound undergoing treatment with compression therapy.
3. Contraindications or hypersensitivity to the use of the ALLEVYN Gentle Border.
4. Participation in the treatment period of another clinical trial within 30 days of Visit 1 or planned participation overlapping with this study.
5. Subjects with skin features (e.g. tattoos, skin color, pre-existing scarring) which, in the opinion of the Investigator, could interfere with the study assessments.
6. Subjects who have participated previously in this clinical trial.

7. Subjects with a history of poor compliance with medical treatment.
8. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

7.4 SCREENING

Participating study sites are required to document all screened subjects considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and noted on the Screening and Enrollment Log. All screening activities that occur prior to consent shall be referred to as pre-screening.

7.5 INFORMED CONSENT

Before conducting any study procedures or examinations, the purpose and nature of the study should be explained to the subject. The subject, will then **read**, **sign**, and **personally date** the EC-approved informed consent document(s). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent document will be provided to the subject, a copy will be placed in the subject's medical record, with the original filed in the Investigator Site File (ISF).

7.6 ENROLMENT

The point of enrolment into the study is when the subject has signed and dated the informed consent document and met all the eligibility criteria.

The anticipated enrolment period for 40 subjects is thirteen (13) months. Once the subject is enrolled a subject ID number will be assigned as a unique study identifier.

7.7 LOST TO FOLLOW-UP

Some actively enrolled subjects will not return for follow-up exams on time. Study personnel must make a reasonable effort to contact the subject and document the following contact attempts

before declaring a subject to be lost to follow-up: the subject has been contacted according to the site's policies, but no fewer than two documented phone contacts and one certified letter without response. Copies of all attempts to reach the subjects by mail or email and/or the attempts to contact the subject via other means should be documented, and that documentation should be kept with the subject's source documents.

7.8 WITHDRAWAL

7.8.1 Withdrawal from Treatment

If a subject is withdrawn from study treatment the Treatment Discontinuation Case Report Form (CRF) needs to be filled out. However, the subjects will be followed up to the end of the study for safety assessments until day 28 (± 3 days).

Subjects may be withdrawn early from study treatment based on the decision of the investigator. This might include but is not limited to the following reasons:

- Closure of the reference wound
- Worsening condition of reference wound
- If the subject misses two (2) consecutive dressing changes/study visits, interrupting treatment for longer than seven (7) days
- A change in treatment that is clinically warranted
- An adverse event (AE)
- Concurrent illness
- Adverse device effects (ADE)
- Non-compliance (e.g. did not follow instructions)
- Lost to follow-up (LTFU)
- Any other significant reason identified by the Investigator

Any subject that does not meet the minimum reference wound size requirement following wound size tracing at Visit 1 will be withdrawn. Subjects withdrawn from the study for this reason alone shall be replaced by enrolment of a new study subject. A new subject number will be assigned.

7.8.2 Subject's Withdrawal of Consent to Participate in Study

Study participation is voluntary, and subjects may withdraw at any point during the study without giving their reason for doing so. Where subjects withdraw consent, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's privacy. The reason for withdrawal will be recorded in the CRF and source documents.

7.8.3 Use of Data Following Withdrawal

In cases where the subject withdraws consent, the data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected.

8. STUDY DESIGN

8.1 STUDY DESIGN

This is a non-randomized, open label study in up to 8 study centres at maximum, conducted in up to 3 countries in Europe. The sample size is 40 subjects. There is no comparator group, however, subjects will be consecutively enrolled into 2 wound groups: A minimum of 10 subjects with acute wounds and a minimum of 10 subjects with chronic wounds.

Participation in the study will last 4 weeks (28±3 days) for each subject. All subjects will receive ALLEVYN Gentle Border as the study device, there is no control group. Subjects will be required to make at least one visit per week to the study center.

In total, 5 study visits are planned for each subject (day 0, day 7, day 14, day 21, day 28). The primary clinical endpoint (reduction of wound size) will be assessed at each study visit by using a specific camera. This camera will make a photograph of the wound in a standardized manner and will calculate the wound length, wound width and the depth of the wound automatically.

8.1.1 Treatment Allocation

This study is not randomized.

8.1.2 Blinding

This study is an open label post-market clinical follow-up study.

8.2 STUDY ENDPOINTS

8.2.1 Primary Endpoint

The absolute reduction in wound area from baseline to end of study visit.

8.2.2 Secondary Endpoints

- Absolute reduction in area from baseline to days 7(+/-3), 14 (+/-3), 21 (+/-3)
- Absolute reduction in depth and volume from baseline to visits 2, 3, 4 and end of study visit
- Percentage reduction in area, depth and volume from baseline visit to visits 2, 3, 4 and end of study visit
- Exudate management (fluid handling ability including leakage and percentage strikethrough)
- Exudate type, amount and viscosity
- Odour control – during wear and during dressing change
- Dressing change frequency
- Condition of surrounding skin
- Signs of clinical infection
- Healing of reference wound
- Dressing wear time
- Dressing retention, presence of bunching up and percentage dressing lift
- Comfort during wear
- Showerproof qualities
- Pain on application, during treatment and on dressing removal

Patient Reported Outcome (PRO):

- To assess the change from baseline in subject reported outcomes using the Cardiff Wound Impact Schedule (CWIS)

Safety Performance:

- All Adverse Events and Device Deficiencies

8.2.3 Other Endpoints

Not applicable.

8.3 Methods Used to Minimize Bias and Maximize Validity

The study will be conducted across multiple centres and subjects will be enrolled by wound type to safeguard against major imbalances in clinical characteristics at baseline and aid comparability between the wound groups.

9. STUDY PROCEDURES

9.1 Visits and Examinations

9.1.1 Summary

All subjects receive the ALLEVYN Gentle Border study device at visit 1 (Baseline, day 0). In total, all subjects need to perform 5 key study visits between week 1 and week 4, as shown in table 1. The visit schedule is based on the 7 days of maximum dressing wear time of ALLEVYN Gentle Border. The key visit date is counted from Baseline (day 0) and usually occurs on the same weekday in the following week. If a dressing change is required between the key visits the subject should come to an interim on-site visit (Routine Dressing Change Visit). A routine dressing change assessment will then be performed and documented in the Case Report Form. Then the subject

continues with the next study key visit, counted from Baseline. If a subject is withdrawn from AGB treatment prior to key visit 5, this subject is still regarded as an active study participant. He/she should continue to come to the study key visit to follow-up with patients' safety up to visit 5.

9.1.2 Study Visit 1 - Initial Visit (Baseline Visit, day 0)

The following assessment will be performed at Visit 1.

1. Obtain written informed consent from the subject as detailed in Section 7.5.

   ----- Do not proceed until consent has been obtained -----
2. Screen the subject for protocol inclusion/exclusion criteria and identify the study wound as the "reference wound" (if more chronic wounds are present per subject).
3. Assign the subject to a study number.
4. Provide the subject with the pages of CWIS and Patient Pain Scale, and allow sufficient time to complete it.
5. Classify the wound type and perform wound assessment according to the Bates-Jensen Wound Assessment Tool (BWAT), as outlined in chapter 9.2.4.
6. **Photograph the wound** with the delivered digital camera (Silhouette) and make sure that the image is assigned to the correct patient.
7. Apply ALLEVYN Gentle Border dressing on the wound.
8. Record details of the size and order number of ALLEVYN Gentle Border (including dressing cut, if performed). ALLEVYN Gentle Border can be cut and an aseptic technique should be used with cutting the dressing. Ensure any exposed foam areas are covered with an appropriate film dressing taking care not to cover the entire dressing.
9. Assess the ease of applying the dressing, including remains in place and repositioning (if applicable).
10. Instruct the subject to carefully follow the standard care instructions until the next dressing change and provide information concerning arrangements for future study visits. Subjects should return to the study center for the next study visit in 7 days (± 3), or earlier if a dressing change is required.

11.	Record the total time that the subject spent at the visit (start to finish of wound care procedures).

9.1.3 Study Visit 2 (day 7, ±3), Visit 3 (day 14, ±3), Visit 4 (day 21, ±3)

Visits 2 - 4 will be performed as on-site visits, so the subjects need to be present at each key study time point. These visits should take place every seventh (7) day. In case a dressing change is required before day 7, the instructions for a Routine Dressing Change Visit need to be followed (chapter 9.1.4).

Subjects who are already withdrawn from treatment and no longer require a dressing change shall be followed up on the study visits to collect safety information.

1.	Question subjects regarding any changes in health or concomitant treatment.
2.	Hand out the CWIS, Patient Assessment Scale and Pain Scale to the subject and allow sufficient time to complete it.
3.	Photograph the dressing in situ prior to removal with the delivered digital camera.
4.	Remove the old dressing and inspect the wound. Complete a wound assessment according to BWAT (see Section 9.2.4).
5.	Assess the reason for dressing change, assess the ease of dressing removal and dressing leakage.
6.	Record any debridement and the method of debridement, and **take a photograph of the wound immediately prior to and following debridement.** *Note: Photographs are not necessary if the subject was withdrawn from treatment at a previous visit.*
7.	Redress the wound, if clinically indicated.
8.	Record details of all dressings used (e.g. brand, size, etc.) as well as any treatment applied underneath the dressing.

9. Assess the ease of applying the new dressing, including remains in place and repositioning (if applicable).
10. Instruct the subject to carefully follow the ulcer care instructions until the next dressing change and provide information concerning arrangements for future study visits.
11. Record the total time that the subject spent at the visit (start to finish of ulcer care procedures).
12. If any AE or DevD are observed or reported after application of study product, they must be reported as instructed in Section 12 (Adverse Events and Device Deficiencies).

9.1.4 Routine Dressing Change Visit (between key study visits, if required)

As ALLEVYN Gentle Border has a maximum recommended wear time of 7 days, routine dressing changes might occur between scheduled study visits. **Dressings should not be given to study subjects; the dressing should only be changed by the investigator or delegated person.**

If a subject requires dressing change in between a study visit, the following assessments will be performed.

1. Question subjects regarding any changes in health or concomitant treatment.
2. Ask the subject to assess the comfort of wearing the dressing since the last visit.
3. Photograph the dressing in situ prior to removal with the delivered digital camera.
4. Remove the old dressing, inspect the wound and complete wound assessment according to BWAT (see Section 9.2.4).
5. Assess the reason for dressing change, assess the ease of dressing removal and dressing leakage.
6. Record any debridement and the method of debridement, and **take a photograph of the wound immediately prior to and following debridement.**
7. Assess the level of pain experienced by the subject when the dressing is removed.

8. Redress the wound, if clinically indicated.
9. Record details of all dressings used (e.g. brand, size, etc.) as well as any treatment applied underneath the dressing.
10. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Safety Section 12.
11. Redress the wound with ALLEVYN Gentle Border.
12. Record details of the new ALLEVYN Gentle Border dressing.

9.1.5 End of Study Visit (day 28, ±3)

The End of Study Visit will be performed as an on-site visit. This should coincide with the normal timing of dressing changes, i.e. seven (7) days.

1. Question subjects regarding any changes in health or concomitant treatment.
2. Hand out the CWIS, Patient Assessment Scale and Pain Scale to the subject and allow sufficient time to complete it.
3. Photograph the dressing in situ prior to removal with the delivered digital camera.
4. Remove the old dressing, inspect the wound and complete wound assessment according to BWAT (see Section 9.2.4).
   Note: A full wound assessment is not necessary if the subject has already been withdrawn from treatment.
5. Assess the reason for dressing change, assess the ease of dressing removal and dressing leakage.
6. Record any debridement and the method of debridement, and **take a photograph of the wound immediately prior to and following debridement.**
7. Fill out the Study Completion CRF.

8.	Record the total time that the subject spent at the visit (start to finish of wound care procedures).
9.	If any AE or DD are observed or reported, they must be recorded as instructed in Safety Section 12.

9.1.6 Unscheduled Visits

Visits to the research site for **other reasons** than dressing changes may be captured as an Unscheduled Visit at the discretion of the Investigator with all information recorded in the source documents and on the Unscheduled Visit CRF.

9.1.7 Concomitant Medications and Therapies

A concomitant treatment is any drug, substance or device administered at any time from enrolment into the study through the last study visit.

9.1.7.1 *Concomitant Medications*

9.1.7.1.1 Excluded Concomitant Medications

- Oxidizing agents such as hypochlorite solutions (e.g. EUSOL) or hydrogen peroxide in conjunction with AGB, as these can reduce the absorbency of the dressing.

9.1.7.1.2 Recording Concomitant Medications in the CRF

Concomitant medications meeting the following criteria will be recorded on the CRF:

- All current and past reference wound medication.
- Concomitant medication used to treat the reference wound and the peri-wound area (such as treatment for erythema, irritation, itching), together with the indication for the medication.
- Concomitant medications used to treat all Adverse Events (AE), Serious Adverse Events (SAE), ADE, Serious Adverse Device Effects (SADE) and Unanticipated Serious Adverse Device Effects (USADE).

9.1.7.2 *Concomitant Therapies*

9.1.7.2.1 Therapies Prohibited During the Study

- Negative pressure wound therapy during the study (e.g. PICO)

9.1.7.2.2 Recording Concomitant Therapies in the CRF

Concomitant therapies meeting the following criteria will be recorded on the CRF:

- All current and past reference wound therapies.
- Concomitant therapies used to treat the reference wound and the peri-wound area, together with the indication for the therapy.
- Concomitant medications used to treat all Serious Adverse Events (SAE), ADE, Serious Adverse Device Effects (SADE) and Unanticipated Serious Adverse Device Effects (USADE). Adverse device effects related to administration of these treatments must be documented in the appropriate CRF.

9.1.8 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation in the study, who are withdrawn from the study for reasons of safety or non-compliance, or who are withdrawn from the study for failure to complete the patient scores at Visit 1. Where possible, the Treatment Discontinuation CRF should be completed for all subjects who discontinue the study early. When consent is withdrawn, the date of and reason for discontinuation should be captured.

Subjects may be withdrawn from the study at any time if, in the opinion of the Investigator, their continued participation in the study poses a risk to the subject, as outlined in section 7.8.1.

If appropriate, the Investigator will advise the subject of subsequent therapy and/or procedures necessary for their medical condition, which will consist of standard care.

9.1.9 Subject Pregnancy

Women of child-bearing potential are not excluded from the study. However, if a woman becomes pregnant during the study, S&N must be contacted immediately once the investigator is made aware of the pregnancy and a decision will be made regarding the continuation in the study of the pregnant woman. Pregnancy is not reportable as an adverse event; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis. Pregnancy-related information will be collected until the end of the pregnancy.

9.2 STUDY METHODS AND MEASUREMENTS

9.2.1 Pressure Ulcer Classification

Pressure ulcers should be classified according to the European Pressure Ulcer Advisory Panel 2017 (3).

Stage I: Non-blanchable erythema

Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area. The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Category I may be difficult to detect in individuals with dark skin tones. May indicate “at risk” persons.

Stage II: Partial-thickness

Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled blister. Presents as a shiny or dry shallow ulcer without slough or bruising.* This Category/Stage should not be used to describe skin tears, tape burns, perineal dermatitis, maceration or excoriation.

*Bruising indicates suspected deep tissue injury.

Stage III: Full-thickness skin loss

Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling. The depth of a Category/Stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and Category/Stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage III pressure ulcers. Bone/tendon is not visible or directly palpable.

Stage IV: Full thickness tissue loss

Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunneling. The depth of a Category/Stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and these ulcers can be shallow. Category/Stage IV ulcers can extend into muscle and/or supporting structures (e.g., fascia, tendon or joint capsule) making osteomyelitis possible. Exposed bone/tendon is visible or directly palpable.

9.2.2 Diabetic Foot Ulcer (DFU) Classification

Diabetic foot ulcers should be classified according to SINBAD assessment (5). The SINBAD score represents an ulcer classification system which can be used as a standard measure in international studies. The SINBAD score ranges from 0 to 6 and emphases 6 different elements for DFU classification. The higher the score the higher the grade of DFU. The SINBAD score will be assessed for each subject at baseline visit.

Site	0=Forefoot
	1=Midfoot and Hind Foot
Ischemia	0=Pedal blood flow intact
	1=Reduced pedal blood flow
Neuropathy	0=Sensation intact
	1=Sensation lost

Infection	0=None (bacterial)
	1=Present
Area	0=Ulcer< 1cm²
	1=Ulcer> 1cm²
Depth	0=Ulcer confined to skin and subcutaneous tissue
	1=Ulcer reaching muscle, tendon or deeper

9.2.3 Photographs and Wound Size Measurements

The primary endpoint will be assessed by the wound photographs collected by the delivered digital camera (Silhouette) during each key study visit. This makes sure that photographs can be compared by using a standardized technique. The secondary endpoint information will be derived by the following investigator assessments and by patient questionnaires as listed in this section below.

Photographs:

Wound photographs will be done by the investigator or delegated personnel.

Photographs will be taken for all subjects per visit instructions (see section 9.1) by using the delivered digital camera (Silhouette). The study centers will be trained on the use of the camera prior to start with patient enrolment.

Wound Size Measurement:

The wound size measurements will be performed directly from the wound photographs taken from the wound per each visit. A special digital camera (Silhouette, ARANZ) will be delivered to the study center. The camera will measure the lengths, the depth and the width of the wound automatically. The wound photographs and the resulting wound measures will be stored in a database. A training will be performed prior to start of the study and handling instructions will be provided.

9.2.4 Reference Wound Assessments with modified Bates-Jensen Wound Assessment Tool (BWAT)

Wound assessments will be performed by the investigator at each study visit in alignment with the Bates-Jensen Wound Assessment Tool (4). The Bates-Jensen Wound Assessment Tool provides 13 assessment parameters which will be scored in a defined measure (1). Each score items will be summarized into a total score. The higher the total score, the more severe the wound status. A source data sheet containing each listed score items will be provided to the study centers to document the BWAT on a primary source. The BWAT tool and the instructions can be found in Appendix 21.4.

9.2.5 Patient Assessment Scale

The patient assessment scale (PAS) is a questionnaire that will be filled out by the patient. During the AGB treatment phase, the subject will be asked to answer the following questions at each study visit. The PAS will be entered directly into the case report form and will serve as source data.

1. How have you found your experience in terms of leakage?

   0=Unacceptable level of leakage
   10=No leakage

2. How have you found your experience in terms of the feeling of moisture on your skin underneath the dressing

   0=Unacceptable feeling of moisture
   10=No feeling of moisture on the skin

3. How have you found your experience in terms of odour?

   0=Unacceptable level of odour
   10=No odour

4. How have you found your experience in terms of visible exudate?

   0=Unacceptable level of visible exudate
   10=No visible exudate

5. How protected did the dressing make your wound feel?

   0=Unacceptable level of protection
   10=Very protected
6. How have you found your experience in terms of dressing comfort?

   0=Unacceptable level of comfort
   10=Very comfortable

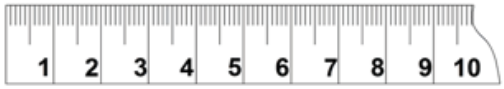
7. How have you found your experience in terms of being able to maintain a normal showering routine? (NA if patient does not have a normal showering routine)

   0=Unacceptable level of impact (unable to bathe)
   10=No negative impact

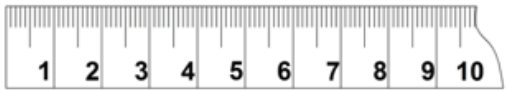
9.2.6 Patient Pain Scale (PPS)

During the AGB treatment phase, the patient will be asked to describe the level of pain during the application, during AGB treatment and on removal of the dressing on a scale from 0 (no pain) to 10 (worst pain). The subject will be asked to draw a vertical line on this visual scale to indicate the value. The value will be rounded to a whole number and transmitted into the CRF by the investigator. The PPS will be entered directly into the case report form and will serve as source data.

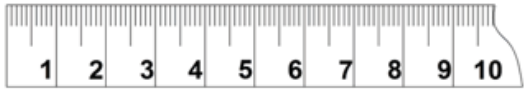
Level of pain experienced by the subject on application of the dressing



Level of pain experienced by the subject during treatment with AGB



Level of pain experienced by the subject on removal of the dressing



9.2.7 Cardiff Wound Impact Questionnaire (CWIS)

The CWIS is a Quality of Life Questionnaire. During the AGB treatment phase, the subject will be asked to fill out the CWIS at each study visit. The CWIS will be entered directly into the case report form and will serve as source data.

The CWIS is a subjective, qualitative measure that covers four domains: physical functional status, symptoms and side effects, social functioning and psychological state. Each line item provides 5 answers. Only one box should be ticked by the subject per line item. The 5-point Likert scale will be counted from 1 to 5 and each domain will be listed separately at the end of the study (6).

1 = Not at all/Not Applicable, 2 = Slightly, 3 = Moderately, 4 = Quite a bit, and 5 = Very

9.2.8 Dressing and Clinical Performance

The following items on dressing and clinical performance will be assessed by the investigator at each study visit.

- Healing of reference wound (yes/no) and signs of clinical infection.
- Dressing comfort (wear comfort, showerproof qualities, odour control)
- Dressing movement (reason for change, adherence to wound, dressing retention, dressing lift or bunching up)
- Dressing performance (leakage, strikethrough, change frequency, wear time, fluid handling ability)
- Exudate evaluation (type, amount, viscosity)
- Pain evaluation (application, during treatment, removal)
- Wound and surrounding skin evaluation

9.2.9 Biological Samples

This study does not require the collection of any biological samples.

9.3 QUALITY OF LIFE

The CWIS is a Quality of Life Questionnaire. During the AGB treatment phase, the subject will be asked to fill out the CWIS at each key study visit.

The Cardiff Wound Impact Schedule (CWIS) is a validated tool for assessing the health-related quality of life of people with venous leg ulcers and diabetic foot ulcers. It is a subjective, qualitative measure that covers three domains:

- Physical symptoms and daily living (24 items, score range: 24-120)
- Social life (14 items, score range: 14-70)
- Well-being (7 items, score range: 7-35)

Each question provides 5 answers and will be counted from 1 (not at all) to 5 (very). Only one box should be ticked by the subject per line item. (6). This instrument also includes two further single item ‘global’ scales for HRQoL and satisfaction with the quality of life.

10. STATISTICAL DESIGN

The following is a brief description of the analyses to be described in this plan. If there are any changes from the analysis described below it will be detailed in the SAP and the Clinical Study Report (CSR). Any changes/additions to the analysis described in the SAP will also be detailed in the CSR.

10.1 GENERAL

Smith & Nephew's Global Biostatistics group will conduct the statistical analysis for this study. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate.

Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, mean, median, standard deviation, minimum and maximum values. All analyses will be performed in SAS 9.4 (or later).
The handling of missing data will be detailed in the SAP.

10.2 ANALYSIS POPULATIONS

The following analysis populations will be used for this study:

- **Safety Population (SAF)**: Including all subjects who enroll in the study and receive the study treatment. This population will be used for analysis of safety.
- **Modified Intention to Treat population (mITT)**: following Intention to Treat principle including all subjects who are enrolled into the study and complete at least one post-baseline assessment. This population will be used for the primary analysis of the primary and secondary endpoints.

- **Per-Protocol Population (PP)**: including all subjects in the mITT, who have no significant protocol deviations and who meet the inclusion/exclusion criteria. This population will be used for a secondary analysis of the primary and secondary endpoints.

10.3 BASELINE DATA

Baseline data to be summarised includes: demographics, relevant medical history, wound type, wound location and duration of reference wound. Baseline data for all primary and secondary endpoints (clinical performance, dressing performance and patient reported outcomes) will be summarised along with the rest of the visits for each particular endpoint.

10.4 EFFICACY ANALYSIS

10.4.1 Analysis of Primary Endpoint

The primary endpoint for this study is the absolute reduction in wound area from baseline to end of study.

The reference wound area will be summarised at each dressing change assessment and study visit. The absolute reduction in the reference wound area from baseline to each post-baseline study visit will also be summarised.

The absolute reduction in area will be analysed as the dependent variable in a repeated measures ANCOVA model. As a minimum the models will contain a term for visit and the following terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: centre, wound type, BMI and baseline area. The estimate LSMean reduction in area from baseline to all study visits will be presented with the associated 95% confidence intervals, with the estimate for the end of study visit (day 28±3) being used for analysis of the primary endpoint.

If the assumptions of ANCOVA are not met then a non-parametric analysis will be considered.

The primary analysis analysis of this endpoint is to be carried out using the mITT population. The same analysis will be carried out on the PP population as a secondary analysis.

10.4.2 Analysis of Secondary Endpoints

All secondary endpoints will be analysed using the mITT population as the primary analysis.

Wound Measurements

The reference wound volume and depth will be summarised at each dressing change assessment and study visit. The absolute reduction in the reference wound volume and depth from baseline to each visit will also be summarised.

The same analysis as the above repeated ANCOVA model is planned to be used to analyse absolute reduction in volume and depth (separately) from baseline to all post-baseline study visits. As well as the summaries of absolute reduction, the percentage reduction in area, volume and depth will also be summarised from baseline to all post-baseline study visits.

Cardiff Wound Impact Schedule (CWIS):

The CWIS consists of three domains: Social Life (CWIS-SL), Wellbeing (CWIS-WB), Physical Symptoms and Daily Living (CWIS-PSDL). For each domain a score from 0-100 is derived with higher scores being better.

Scores for each CWIS domain will be summarised at each study visit by wound type and overall. The increase in score from baseline to each study visit will also be summarised by wound type and overall.

A repeated measures ANCOVA model will be fit separately for each CWIS domain. In each case the domain score will be used as the dependent variable and as a minimum the model will contain a term for visit. The following extra terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: centre, wound type, BMI and baseline domain score. The estimate LSMean increase in domain score from baseline to all study visits will be presented with the associated 95% confidence intervals.

If the assumptions of ANCOVA are not met then a non-parametric analysis will be considered.

Clinical and Dressing Performance

Performance endpoints to be summarised at all study visits and routine dressing changes by wound type and overall include:

- Reference wound healed (yes/no).
- Comfort during wear.
- Odour control – during wear and during dressing change.
- Showerproof qualities.
- Dressing retention, presence of bunching up and percentage dressing lift.
- Pain on application, during treatment and on dressing removal.
- Exudate type, amount and viscosity.
- Exudate management (fluid handling ability including leakage and percentage strikethrough).
- Dressing adherence to wound bed will be cross-tabulated by exudate level at previous dressing assessment.
- Dressing wear time (days) should be summarised for both wear time per subject i.e. take the average wear time for each subject and summarise that and also for the wear time of all dressings used in the study.
- Dressing change frequency will be summarised as the number of dressings per subject.
- Condition of surrounding skin will be summarised at all study visits and routine dressing changes. Also the condition of surrounding skin at each post-baseline study visit will be cross tabulated with condition of surrounding skin at baseline.
- Signs of clinical infection will be summarised at all study visits and routine dressing changes.

10.5 SAFETY ANALYSES

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

Extent of Exposure

The duration of treatment will be summarized.

Adverse Events

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

The number of subjects reporting: adverse events (AE), serious adverse events (SAE), adverse device effects (ADE), serious adverse device effects (SADE) and unanticipated serious adverse effects (USADE) will be summarized. In addition, AEs will be summarised by: severity; the relationship to the investigational device; outcome and duration of adverse events at trial discontinuation.

Further safety summaries may be defined in the SAP.

10.6 INTERIM ANALYSES

Not Applicable

11. SAMPLE SIZE JUSTIFICATION

The sample size determination for this study was based on a previous study (CE/046/ALF) demonstrating an absolute mean reduction in wound area from baseline to 28 days of 3cm^2 with a standard deviation of 5cm^2, in a range of moderate to highly exuding wound types. In order to show a statistically significant reduction in the mean wound area for this study, it was calculated that 26 subjects would achieve 83% power.

Unfortunately, several subjects were recruited into the current study with wounds smaller than 3cm^2, little to no exudate or chronic wounds of less than 6 weeks duration, meaning these wounds are not comparable to the previous study in terms of healing challenge. As a result, protocol modifications have been made to ensure a minimum wound size is included in the inclusion criteria as well as provide an opportunity to re-emphasise the challenging nature of wounds we are seeking to recruit with regards to level of exudate. With this in mind and accounting for the 10 patients enrolled in the study under protocol V2.0 (as at 19 June 2019), it is recommended we

increase the total patient recruitment target to n = 35 patients to ensure we have captured a range of wounds of comparable healing challenge to the previous study.

Using the same assumptions, it can be calculated that 35 subjects would provide 93% power to show a statistically significant reduction in the mean wound area from baseline to 28 days. Analysis for this study will be conducted separately for patients that comply with V3.0 of the protocol and therefore the study is over-powered to allow for greater than 80% power in the V3.0 protocol population.

Allowing for a 15% lost to follow up rate as used previously, 40 subjects will be recruited into this study.

12. ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 DEFINITIONS

The categories of adverse events are shown in table 12.1-1. The definitions for each of these categories are given in the subsequent sections.

Table 3: Categories of Adverse Event

<table>
<tr><th></th><th>NOT DEVICE-RELATED</th><th colspan="2">DEVICE- OR PROCEDURE-RELATED</th></tr>
<tr><td>NON-SERIOUS</td><td>ADVERSE EVENT
(AE)</td><td colspan="2">ADVERSE DEVICE EFFECT
(ADE)</td></tr>
<tr><td rowspan="3">SERIOUS</td><td rowspan="3">SERIOUS ADVERSE EVENT
(SAE)</td><td colspan="2">SERIOUS ADVERSE DEVICE EFFECT
(SADE) (SEE 12.1.3)</td></tr>
<tr><td>ANTICIPATED</td><td>UNANTICIPATED</td></tr>
<tr><td>ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT
(ASADE)</td><td>UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT
(USADE)</td></tr>
</table>

12.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence between enrollment and treatment discontinuation associated with the use of an IP/Ancillary Product, whether or not considered causally related to that IP/Ancillary Product.

AE is used both to refer to AE which are non-serious non-IP or procedure-related and as an umbrella term referring to adverse events of all classifications.

An AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease. For reporting purposes, emphasis is placed first and foremost on whether or not the event constitutes an untoward medical occurrence.

12.1.2 Adverse Device Effect

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

Not Related - An AE is considered to be not related to the use of an IP or the procedure when the effect is DEFINITELY UNRELATED or UNLIKELY to have any relationship to the use of the IP or the procedure;

Related – An AE is considered to be related to the use of an IP or the procedure when there is a POSSIBLE, PROBABLE, or DEFINITE relationship between the AE and the use of the IP or the procedure.

An ADE is further categorized depending on whether the criteria in section 12.1.3 and 12.1.4 are met.

12.1.3 Serious Adverse Events and Serious Adverse Device Effects

An AE or ADE is considered a **Serious** Adverse Event (SAE) or **Serious** Adverse Device Effects (SADE) if, in the view of either the Investigator or the Sponsor, it:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
    - 1) a life-threatening illness or injury, or
    - 2) a permanent impairment of a body structure or a body function, or
    - 3) in-patient or prolonged hospitalization, or
    - 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to foetal distress, foetal death or a congenital abnormality or birth defect

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

12.1.4 Anticipated/Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. Summary of risk analysis report and thus anticipated SADEs is communicated through the IFU and in protocol section 4.3.

12.1.5 Severity

The severity of every AE will be assessed by the PI or medically qualified site staff to whom the responsibility has been delegated and documented on the delegation of authority log. AE should

be classified as mild, moderate, or severe, regardless of whether or not the AE are considered to be serious or non-serious. The classification should be based on the following definitions:

Mild - An event is mild if the subject is aware of, but can easily tolerate the sign or symptom;

Moderate - An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities;

Severe - An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

12.1.6 Device Deficiency

A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DD includes malfunctions, use errors and inadequate labeling.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence
a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,
are considered Device Deficiencies with potential to cause SADE and shall be reported as specified in section 12.3.

12.2 AE Coding Dictionary

The latest version of MedDRA will be used to code AEs.

12.3 REPORTING PROCEDURES

AE of any kind and DD will be recorded in the applicable CRF and source notes. The Investigator will evaluate all AE for relationship to the device and procedure, if applicable, seriousness, and severity. DD will be evaluated for potential to cause SADE. The following timescales should be followed for the AE/DD information to be submitted/entered into the CRF and reported to the Sponsor or designee (see figure 12.2-1):

- ADE and DD – without unreasonable delay
- SAE, SADE and DD with potential to cause SADE – immediately (i.e. within 24 hours of the investigator being informed about the event)

For ADE and DD, details of the product/procedure related to the event will be included and where applicable, pictures taken of the device. The deficient product should be retained for return to S&N unless it is contaminated (e.g., used dressings must not be retained). Updates to submitted information will be recorded in the CRF according to the timescales above.

All adverse events will be reviewed by a medically qualified person appointed by the Sponsor to determine which, if any, meet criteria for expedited reporting to the regulatory authorities.

The investigator will inform the IRB/IEC of adverse events according to the IRB/IEC requirements. Depending on the nature of the adverse event, S&N may request copies of the subject's medical records, Imaging, Operative notes, as well as results of any relevant laboratory tests performed or other documentation related to the AE. If the subject was hospitalized, a copy of the discharge summary may be requested by S&N and should be forwarded as soon as it becomes available. In certain cases, S&N also may request a letter from the Investigator that summarizes the events related to the case. Refer to the ISF Sponsor Contact Information Sheet to report SAE, ADE and SADE, unanticipated SADE, and DD.

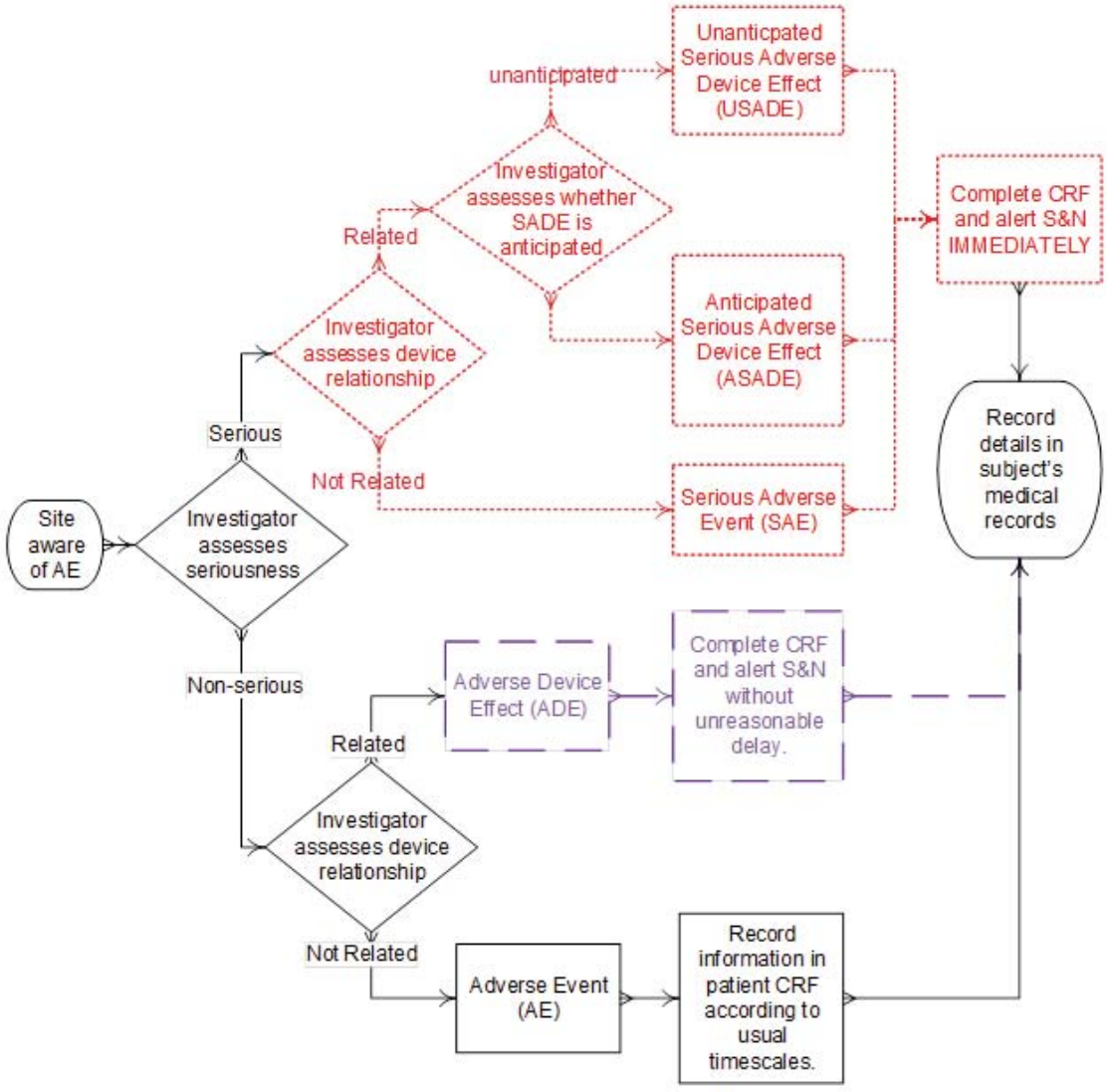


Figure 5: Evaluation and Reporting of AE

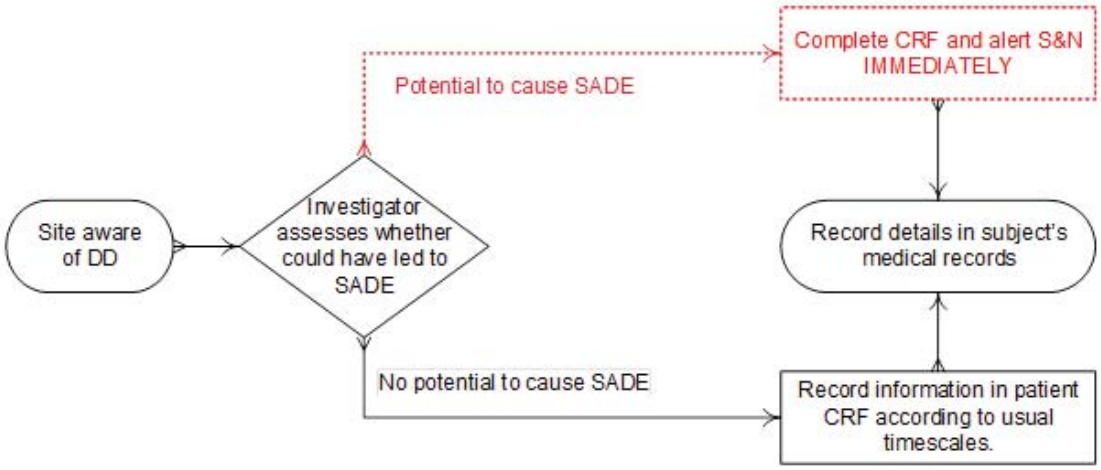


Figure 6: Evaluation and Reporting of DD

12.4 UNBLINDING OF INVESTIGATIONAL PRODUCT

Not applicable.

12.5 FOLLOW-UP OF SUBJECTS WITH ADVERSE EVENTS

For subjects who are experiencing ongoing unresolved AE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit to determine the outcome of the event.

12.5.1 Ongoing Adverse Events at Study Discontinuation

Adverse events which are **related** to a study procedure or S&N IP and are ongoing at the end of subject's participation: The event should be followed until it is either resolved or until the event

has become chronic and is not expected to further improve based on Investigator's review of the event.

Adverse events which are **not related** to a study procedure or S&N IP and are ongoing at the end of subject's participation should be followed for 30 days after discontinuation or if the AE is resolved, whichever is sooner.

At the time of data analysis (e.g., interim or final), an evaluation of ongoing events should take place and be listed as ongoing in the safety table.

13. INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with the commitments outlined in the study protocol and in the Clinical Trial Agreement provided by the Sponsor, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix 21.9 of this protocol.

14. SPONSOR AND MONITOR RESPONSIBILITIES

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

Detailed monitoring requirements will be documented in the Clinical Monitoring Plan for this study.

14.1 CONTRACT RESEARCH ORGANIZATION

The Sponsor has engaged Contract Research Organization (CRO) to assist in conducting this study. When appropriate, the CRO is referred in study documents as "Sponsor's agent."

14.2 SITE QUALIFICATION VISIT

A site qualification visit may be performed by the Sponsor prior to the execution of a clinical agreement to ensure that all Investigators have the appropriate training, staff, facilities, and resources to adequately conduct the study.

14.3 SITE INITIATION VISIT

A site initiation visit to provide training on the specifics of the study, site obligations and expectations of study conduct will be performed by the Sponsor or qualified person designated by the Sponsor following the execution of the CTA and documented EC approval.

14.4 SPONSOR AUDITS AND REGULATORY INSPECTION

Quality Assurance auditors, whether an employee of the Sponsor or its designee, may evaluate study conduct at the study sites. These parties must have access to any and all study reports and source documentation, regardless of location and format.

14.5 CLOSE-OUT VISIT

A study close-out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries. During study close-out, the monitor will review investigator files to ensure required documents and records are on file, confirm the disposition of any other ancillary items used for the study, and review regulatory requirements regarding records retention and EC reporting requirements.

15. PROTOCOL AMENDMENTS

Amendments should be made only in exceptional cases once the study has started. Protocol amendments must be approved by the protocol signatories prior to submission to the EC. Protocol amendments need to be approved by the EC and Regulatory Authority(ies), as applicable prior to implementation at the site.

16. CONFIDENTIALITY OF THE STUDY

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

17. STATEMENTS OF COMPLIANCE

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki 2016; and ISO 14155:2011 Clinical investigation of medical devices – Good Clinical Practice.

This clinical study will not commence until the required approval/favorable opinion from the EC or regulatory authority has been obtained. Any additional requirements imposed by the EC or regulatory authority will be followed.

Public/Products Liability Insurance has been purchased by Smith & Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies. The Sponsor agrees to operate in good faith and in accordance with ABHI (Association of British Healthcare Industries) guidelines regarding compensation for injury arising in the course of clinical studies.

18. END OF STUDY

The end of the study is defined as the last visit of the last subject undergoing treatment in the study. ALLEVYN Gentle Border is a commercially available product and therefore should be available to subjects after their participation in this study. Subjects may participate for a maximum total duration of 28 (±3) days.

Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g. safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g. departure of Investigator, non-compliance) then this will be undertaken according to the SOPs of the Sponsor.

19. PUBLICATION POLICY

19.1 PUBLICATION OF STUDY DATA

The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the Clinical Trial Agreements between the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws.

19.2 DATA SHARING

Smith & Nephew is committed to upholding the highest ethical and legal standards involved in conducting clinical trials. Smith & Nephew, therefore, supports the data sharing requirements of The International Committee of Medical Journal Editors (ICMJE) published on the 6th June 2017. In accordance, Smith & Nephew will consider requests to share individual (de-identified) participant data that underlie the results of any interventional clinical trial, as presented from the 1st July 2018 within an ICMJE associated journal. Requests made by researchers who provide a methodologically sound proposal will be considered. Requests may include data that underlie results presented in text, tables, figures, and appendices, together with data dictionaries. Availability of these data will begin nine months and end 36 months after article publication. Data supplied may only be used by the researcher(s) named in the approved research proposal for the purposes of achieving the aims of the analyses specified therein. All proposals should be directed to datasharing.gcs@smith-nephew.com. To gain access, data requestors will need to sign a data access agreement.

20. REFERENCES

1. B. SCB-J. Tools to measure wound healing. Wound Care: A Collaborative Practice Manual Wolters Kluwer Health, Philadelphia. 2007:Chapter 6, p. 159.
2. Callaghan R. Case series evaluation: the use of Allevyn Gentle Border Multisite on chronic wounds. Wounds UK. 2012;8(4).
3. EPUAP. Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. 2014:12-3.

4. Harris C, Bates-Jensen B, Parslow N, Raizman R, Singh M, Ketchen R. Bates-Jensen wound assessment tool: pictorial guide validation project. J Wound Ostomy Continence Nurs. 2010;37(3):253-9.
5. Hurd T, Gregory L, Jones A, Brown S. A multi-centre in-market evaluation of ALLEVYN ◊ Gentle Border. Wounds UK. 2009;5(3):32-44
6. P. I, ZG. A. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes Care. 2008;May.
7. Price P, Harding K. Cardiff Wound Impact Schedule: the development of a condition-specific questionnaire to assess health-related quality of life in patients with chronic wounds of the lower limb. Int Wound J. 2004;1(1):10-7.
8. Grothier L. Gentle foam dressings: interim results of an evaluation of the Allevyn range. Br J Nurs. 2009;18(11):S12, S4, S6 passim
9. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009;17(6):763-71.
10. Smith&Nephew. Clinical Evaluation Report ALLEVYN Gentle Border. 2017.
11. Smith&Nephew. Summary of Results CE/046/ALF. 2014.

21. APPENDICES

21.1 PROTOCOL AMENDMENT

21.1.1 General Purposes

a. The following minimum wound size requirement to be added to the inclusion criteria:
   - Presence of a moderately to highly exuding wound of at least 3cm^2 in size.

b. The sample size and number of sites will be increased to ensure capturing a range of wounds of comparable healing challenge to a previous study.

c. The French Ethics Committee reviewed the study and made the following request for changes on protocol.
   - To add bibliographic references of randomized studies evaluating the effectiveness of the medical device.

d. To remove the Patient Assessment Scale, one of the patient reported outcome measurement tools, at Baseline visits.

21.1.2 Rationale

Regarding Purpose (a), to ensure the wound can be evaluated for up to 4 weeks a revision to the current inclusion criteria is required with the need for the wound area to be at least 3 cm^2. The minimum wound size of 3cm^2 has been determined based on wound progression observed in previous similar clinical wound healing studies. Including a minimum wound size will ensure that we are collecting pertinent data regarding dressing performance for both chronic and acute wounds over the entire 4-week treatment period.

Regarding Purpose (b), the sample size determination for this study was based on a previous study demonstrating an absolute mean reduction in wound area of 3cm^2 in a range of moderate to highly exuding wound types. Unfortunately several subjects were recruited into the current study with wounds smaller than 3cm^2, little to no exudate or did not satisfy the inclusion criteria of being chronic wounds (pressure ulcers, leg ulcers or diabetic foot ulcers) of at least 6 weeks duration.

As a result, this modification is going to ensure a minimum wound size is included in the inclusion criteria as well as provide an opportunity to re-emphasise the challenging nature of wounds aimed to be recruited with regards to the level of exudate. Increasing the total patient recruitment target to n= 40 subjects is aiming to ensure to capture a range of wounds of comparable healing challenge to the previous study.

Regarding Purpose (c), additional references and explanations were added to address the request from the French Ethics Committee.

Regarding Purpose (d), the questions in the Patient Assessment Scale are more applicable following the use of ALLEVYN Gentle Border dressing rather than before the treatment with ALLEVYN Gentle Border.

21.1.3 Effect on Study Status

The amendment does not have impacts on the conduct of the study.

21.1.4 Details

The changes listed in Section 21.1.1 are made across the protocol respectively as listed in details below. A reminder to the aseptic technique and dressing precaution was added to where cutting the dressing is allowed being mentioned, i.e. Sections 7.2 and 9.1.2. In Section 10.4.1 Analysis of Primary Endpoint, the percentage reduction in wound area was mistakenly mentioned, it is corrected to absolute reduction in wound area, as percentage is covered as a secondary endpoint. Study team members are updated to reflect the change of Smith & Nephew personnel. The study schedule at Section 2 and 6 are updated to reflect the protocol design and information from the IFU accurately. It is clarified in Section 9 that the patient reported outcomes will be entered directly into the case report form and will serve as source data. The extra blank page was deleted after page 2.

Section	Current Text 10/OCT/2018 Version 2.0	Revised Text 19/JUN/2019 Version 3.0
2. Synopsis	Sample Size: 30 Subjects Number of Study Sites: 2-6 study sites Statistical Rationale: It is assumed that the actual reduction in the mean wound area from baseline to 28 days is 3cm^2 with a standard deviation of 5cm^2. Assuming this data holds true it can be calculated that 26 subjects would provide 83% power to show a statistically significant reduction in the mean wound area from baseline to 28 days. Allowing for a 15% lost to follow up rate, 30 subjects will be recruited into this study. - -	40 subjects Up to 8 study sites It is assumed that the actual reduction in the mean wound area from baseline to 28 days is 3cm^2 with a standard deviation of 5cm^2. Assuming this data holds true it can be calculated that 26 subjects would provide 83% power to show a statistically significant reduction in the mean wound area from baseline to 28 days. Accounting for the protocol modifications outlined in Section 21, it is recommended to increase the total patient recruitment target to 35 subjects, providing 93% power. Allowing for a 15% lost to follow up rate, 40 subjects will be recruited into this study. Added to the Inclusion Criteria: 5. Presence of a moderately to highly exuding wound of at least 3cm^2 in size. Added to Point 7 of the Inclusion Criteria: ALLEVYN Gentle Border can be cut and an aseptic technique should be used with cutting the dressing. Ensure any exposed foam areas are covered with an appropriate film dressing taking care not to cover the entire dressing. The Study Schedule table is updated to accurately reflect the study events

		as shown in the later part of Section 21.1.4. Details.
4. INTRODUCTION	30 subjects	40 subjects
4.1 Literature Summary	-	Added a second paragraph: In addition, several clinical studies utilising AGB have been identified demonstrating evidence of the safety and performance of AGB in wound management. A previous comparative clinical study evaluating the use of AGB compared to a competitor dressing demonstrated the safe and effective use in 21 patients with chronic and acute wounds. No major safety issues were highlighted with either dressing and clinicians were satisfied with exudate handling in all AGB dressing changes. (10). A study by Grothier et al. (2009) showed that AGB was rated highly by the investigating clinicians, with an 87% level of acceptance for the range of clinical indications treated. Satisfaction with the dressing's exudate management was reported in 86% of dressing changes. Another case series, including 153 patients, demonstrated that the AGB dressing was effective in improving wound outcomes, in particular reducing wound area, depth and level of exudate in routine clinical practice. Significant reduction in wound area and depth by the final assessment was observed ($p<0.001$; Hurd et al, 2009). Both of these studies, alongside many others (including comparative studies), have demonstrated the safe and effective use of ALLEVYN Gentle Border in wound management (10).

6.1.1. Investigational Product	The regular shaped ALLEVYN Gentle Border dressing can be left in place for up to seven days, depending on the condition of the wound and the surrounding skin or until exudate is visible and approaches to within 1.5cm of the edge of the dressing pad, whichever is sooner.	The regular shaped ALLEVYN Gentle Border dressing can be left in place for up to seven days, depending on the condition of the wound and the surrounding skin or until exudate is visible and approaches to within 0.5cm of the edge of the dressing pad, whichever is sooner.
6.1.3 Ancillary Product	No ancillary products are to be provided.	INTRASITE Gel will be provided on request for necrotic or sloughy wounds.
6.1.6 Dressing Change	Dressings can be left in place for up to 7 days depending on the condition of the wound and the surrounding skin or until exudate is visible and approaches to within 1.5cm of the edge of the dressing pad, whichever is sooner. Exudate within 1.5cm of the edge of the pad requires changing	Dressings can be left in place for up to 7 days depending on the condition of the wound and the surrounding skin or until exudate is visible and approaches to within 0.5cm of the edge of the dressing pad, whichever is sooner. Exudate within 0.5cm of the edge of the pad requires changing
7.1 SUBJECT POPULATION	Thirty adult subjects	Forty adult subjects
7.2 Inclusion Criteria	- -	<u>Added to the Inclusion Criteria:</u> 5. Presence of a moderately to highly exuding wound of at least 3cm^2 in size. <u>Added after Point 7 in the Inclusion Criteria:</u> ALLEVYN Gentle Border can be cut and an aseptic technique should be used with cutting the dressing. Ensure any exposed foam areas are covered with an appropriate film dressing taking care not to cover the entire dressing.

7.6 ENROLMENT	30 subjects	40 subjects
7.8.1. Withdrawal from Treatment		Any subject that does not meet the minimum reference wound size requirement following wound size tracing at Visit 1 will be withdrawn. Subjects withdrawn from the study for this reason alone shall be replaced by enrolment of a new study subject. A new subject number will be assigned.
8.1 Study Design	This is a non-randomized, open label study in 6 study centers at maximum, conducted in 1-2 countries in Europe. 30 subjects will be enrolled during an enrollment period of 13 months. There is no comparator group, however, subjects will be consecutively enrolled into 2 wound groups: A minimum of 10 subjects of acute surgical or traumatic wounds and a minimum of 10 subjects by chronic wounds.	This is a non-randomized, open label study in up to 8 study centres at maximum, conducted in up to 3 countries in Europe. The sample size is 40 subjects. There is no comparator group, however, subjects will be consecutively enrolled into 2 wound groups: A minimum of 10 subjects with acute wounds and a minimum of 10 subjects with chronic wounds.
9.1.2 Study Visit 1 - Initial Visit (Baseline Visit, day 0)	4. Provide the subject with copies of the CWIS, Patient Assessment Scale and Pain Scale, and allow sufficient time to complete it. -	4. Provide the subject with the pages of CWIS and Patient Pain Scale, and allow sufficient time to complete it. <u>Added after point 8:</u> ALLEVYN Gentle Border can be cut and an aseptic technique should be used with cutting the dressing. Ensure any exposed foam areas are covered with an appropriate film dressing taking care not to cover the entire dressing.
9.2.5. Patient Assessment Scale	-	<u>Added:</u> The PAS will be entered directly into the case report form and will serve as source data.

9.2.6. Patient Pain Scale	-	Added: The PPS will be entered directly into the case report form and will serve as source data.
9.2.7. Cardiff Wound Impact Questionnaire (CWIS)	-	Added: The CWIS will be entered directly into the case report form and will serve as source data.
10.4.1 Analysis of Primary Endpoint	The primary endpoint for this study is the percentage reduction in wound area from baseline to the end of study visit (28±3 days).	The primary endpoint for this study is the absolute reduction in wound area from baseline to end of study.
11. Sample Size Justification	To calculate sample size for this study it is assumed that the actual reduction in the mean wound area from baseline to 28 days when using the dressing is 3cm^2 with a standard deviation of 5cm^2, this is in line with previous results seen in CE/046/ALF and allowing for marginal differences between study dressings. Assuming this data holds true it can be calculated that 26 subjects would provide 83% power to show a statistically significant reduction in the mean wound area from baseline to 28 days. Allowing for a 15% lost to follow up rate, 30 subjects will be recruited into this study.	The sample size determination for this study was based on a previous study (CE/046/ALF) demonstrating an absolute mean reduction in wound area from baseline to 28 days of 3cm^2 with a standard deviation of 5cm^2, in a range of moderate to highly exuding wound types. In order to show a statistically significant reduction in the mean wound area for this study, it was calculated that 26 subjects would achieve 83% power. Unfortunately, several subjects were recruited into the current study with wounds smaller than 3cm^2, little to no exudate or chronic wounds of less than 6 weeks duration, meaning these wounds are not comparable to the previous study in terms of healing challenge. As a result, protocol modifications have been made to ensure a minimum wound size is included in the inclusion criteria as well as provide an opportunity to re-emphasise the challenging nature of wounds we are seeking to recruit with regards to level of exudate. With this

		in mind and accounting for the 10 patients enrolled in the study under protocol V2.0 (as at 19 June 2019), it is recommended we increase the total patient recruitment target to n = 35 patients to ensure we have captured a range of wounds of comparable healing challenge to the previous study. Using the same assumptions, it can be calculated that 35 subjects would provide 93% power to show a statistically significant reduction in the mean wound area from baseline to 28 days. Analysis for this study will be conducted separately for patients that comply with V3.0 of the protocol and therefore the study is over-powered to allow for greater than 80% power in the V3.0 protocol population. Allowing for a 15% lost to follow up rate as used previously, 40 subjects will be recruited into this study.
20. References	-	<u>Added the references listed below and consequent updates to reference numbering throughout the protocol:</u> 5. Hurd T, Gregory L, Jones A, Brown S. A multi-centre in-market evaluation of ALLEVYN ◊ Gentle Border. Wounds UK. 2009;5(3):32-44 8. Grothier L. Gentle foam dressings: interim results of an evaluation of the Allevyn range. Br J Nurs. 2009;18(11):S12, S4, S6 passim 11. Smith&Nephew. Summary of Results CE/046/ALF. 2014.

Updated STUDY SCHEDULE:

Table 4: Study Visits and Assessments

Schedule of Events	Key Visits					Other Visits	
	Visit 1 (Baseline) Day 0	Visit 2 Day 7 (+/-3)	Visit 3 Day 14 (+/-3)	Visit 4 Day 21 (+/-3)	End of Study Visit 5 Day 28 (+/-3)	Routine Dressing Changes	Treatment Discontinuation *(before end of study)*
Informed Consent	√						
Demographics/ Medical History	√						
Verify Inclusion/ Exclusion Criteria	√						
Allocate Study ID Number	√						
Concomitant Medication	√	√	√	√	√	√	√
CWIS Patient Questionnaire	√	√	√	√	√		√
Patient Pain Scale	√	√	√	√	√	√	
Patient Assessment		√	√	√	√	√	
Wound Assessment	√	√	√	√	√	√	√
Photograph Dressing in situ Before Removal		√	√	√	√	√	√
Dressing Change		√	√	√		√	
Photograph Wound Before Dressing Application	√	√	√	√	√	√	√

Schedule of Events	Key Visits					Other Visits	
	Visit 1 (Baseline) Day 0	Visit 2 Day 7 (+/-3)	Visit 3 Day 14 (+/-3)	Visit 4 Day 21 (+/-3)	End of Study Visit 5 Day 28 (+/-3)	Routine Dressing Changes	Treatment Discontinuation *(before end of study)*
Dressing Performance	√	√	√	√	√	√	
Adverse Event (AE) Assessment	√	√	√	√	√	√	√
Record Device Deficiencies (DD)	√	√	√	√	√	√	√
End of Study /Exit Form					√		√

21.2 INSTRUCTIONS FOR USE

Not attached to this protocol. Will be delivered with each ALLEVYN Gentle Border package in its most current version.

21.3 EQUIPMENT AND SPECIAL INSTRUCTIONS

Not applicable.

21.4 BATES-JENSEN WOUND ASSESSMENT TOOL AND INSTRUCTIONS FOR USE

General Guidelines:

Fill out the attached rating sheet to assess a wound's status after reading the definitions and methods of assessment described below. Evaluate once a week and whenever a change occurs in the wound. Rate according to each item by picking the response that best describes the wound and entering that score in the item score column for the appropriate date. When you have rated the wound on all items, determine the total score by adding together the 13-item scores. The HIGHER the total score, the more severe the wound status. Plot total score on the Wound Status Continuum to determine progress.

Specific Instructions:

1. **Size**: Use ruler to measure the longest and widest aspect of the wound surface in centimeters; multiply length x width.

2. **Depth**: Pick the depth, thickness, most appropriate to the wound using these additional descriptions:
   - 1 = tissues damaged but no break in skin surface.
   - 2 = superficial, abrasion, blister or shallow crater. Even with, &/or elevated above skin surface (e.g., hyperplasia).
   - 3 = deep crater with or without undermining of adjacent tissue.
   - 4 = visualization of tissue layers not possible due to necrosis.
   - 5 = supporting structures include tendon, joint capsule.

3. **Edges**: Use this guide:

Indistinct, diffuse	=	unable to clearly distinguish wound outline.
Attached	=	even or flush with wound base, no sides or walls present; flat.
Not attached	=	sides or walls are present; floor or base of wound is deeper than edge.
Rolled under, thickened	=	soft to firm and flexible to touch.
Hyperkeratosis	=	callous-like tissue formation around wound & at edges.
Fibrotic, scarred	=	hard, rigid to touch.

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

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

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

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

7. **Exudate Type**: Some dressings interact with wound drainage to produce a gel or trap liquid. Before assessing exudate type, gently cleanse wound with normal saline or water. Pick the exudate type that is predominant in the wound according to color and consistency, using this guide:

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

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

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

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

10. **Peripheral Tissue Edema & Induration**: Assess tissues within 4cm of wound edge. Non-pitting edema appears as skin that is shiny and taut. Identify pitting edema by firmly pressing a finger down into the tissues and waiting for 5 seconds, on release of pressure, tissues fail to resume previous position and an indentation appears. Induration is abnormal firmness of tissues with margins. Assess by gently pinching the tissues. Induration results in an inability to pinch the tissues. Use a transparent metric measuring guide to determine how far edema or induration extends beyond wound.

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

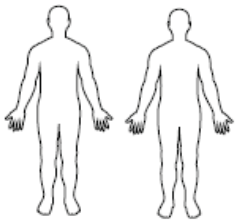
12. **Epithelialization**: Epithelialization is the process of epidermal resurfacing and appears as pink or red skin. In partial thickness wounds it can occur throughout the wound bed as well as from the wound edges. In full thickness wounds it occurs from the edges only. Use a transparent metric measuring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

BATES-JENSEN WOUND ASSESSMENT TOOL NAME

Complete the rating sheet to assess wound status. Evaluate each item by picking the response that best describes the wound and entering the score in the item score column for the appropriate date.

Location: Anatomic site. Circle, identify right (**R**) or left (**L**) and use "**X**" to mark site on body diagrams:

____ Sacrum & coccyx ____ Lateral ankle
____ Trochanter ____ Medial ankle
____ Ischial tuberosity ____ Heel Other Site



Shape: Overall wound pattern; assess by observing perimeter and depth.

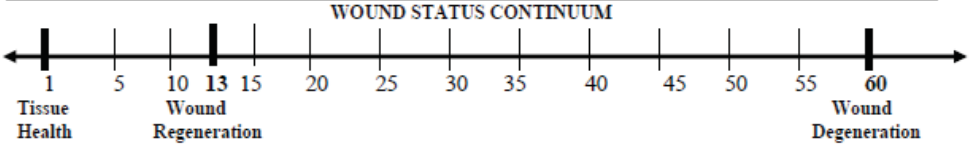
Circle and date appropriate description:

____ Irregular ____ Linear or elongated
____ Round/oval ____ Bowl/boat
____ Square/rectangle ____ Butterfly Other Shape

Item	Assessment	Date Score	Date Score	Date Score
1. Size	1 = Length x width <4 sq cm 2 = Length x width 4--<16 sq cm 3 = Length x width 16.1--<36 sq cm 4 = Length x width 36.1--<80 sq cm 5 = Length x width >80 sq cm			
2. Depth	1 = Non-blanchable erythema on intact skin 2 = Partial thickness skin loss involving epidermis &/or dermis 3 = Full thickness skin loss involving damage or necrosis of subcutaneous tissue; may extend down to but not through underlying fascia; &/or mixed partial & full thickness &/or tissue layers obscured by granulation tissue 4 = Obscured by necrosis 5 = Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures			
3. Edges	1 = Indistinct, diffuse, none clearly visible 2 = Distinct, outline clearly visible, attached, even with wound base 3 = Well-defined, not attached to wound base 4 = Well-defined, not attached to base, rolled under, thickened 5 = Well-defined, fibrotic, scarred or hyperkeratotic			
4. Under-mining	1 = None present 2 =Undermining < 2 cm in any area 3 = Undermining 2-4 cm involving < 50% wound margins 4 = Undermining 2-4 cm involving > 50% wound margins 5 = Undermining > 4 cm or Tunneling in any area			
5. Necrotic Tissue Type	1 = None visible 2 = White/grey non-viable tissue &/or non-adherent yellow slough 3 = Loosely adherent yellow slough 4 = Adherent, soft, black eschar 5 = Firmly adherent, hard, black eschar			
6. Necrotic Tissue Amount	1 = None visible 2 = < 25% of wound bed covered 3 = 25% to 50% of wound covered 4 = > 50% and < 75% of wound covered 5 = 75% to 100% of wound covered			
7. Exudate Type	1 = None			

Item	Assessment	Date Score	Date Score	Date Score
	2 = Bloody 3 = Serosanguineous: thin, watery, pale red/pink 4 = Serous: thin, watery, clear 5 = Purulent: thin or thick, opaque, tan/yellow, with or without odor			
8. Exudate Amount	1 = None, dry wound 2 = Scant, wound moist but no observable exudate 3 = Small 4 = Moderate 5 = Large			
9. Skin Color Surrounding Wound	1 = Pink or normal for ethnic group 2 = Bright red &/or blanches to touch 3 = White or grey pallor or hypopigmented 4 = Dark red or purple &/or non-blanchable 5 = Black or hyperpigmented			
10. Peripheral Tissue Edema	1 = No swelling or edema 2 = Non-pitting edema extends <4 cm around wound 3 = Non-pitting edema extends ≥4 cm around wound 4 = Pitting edema extends < 4 cm around wound 5 = Crepitus and/or pitting edema extends ≥4 cm around wound			
11. Peripheral Tissue Induration	1 = None present 2 = Induration, < 2 cm around wound 3 = Induration 2-4 cm extending < 50% around wound 4 = Induration 2-4 cm extending ≥ 50% around wound 5 = Induration > 4 cm in any area around wound			
12. Granulation Tissue	1 = Skin intact or partial thickness wound 2 = Bright, beefy red; 75% to 100% of wound filled &/or tissue overgrowth 3 = Bright, beefy red; < 75% & > 25% of wound filled 4 = Pink, &/or dull, dusky red &/or fills ≤ 25% of wound 5 = No granulation tissue present			
13. Epithelialization	1 = 100% wound covered, surface intact 2 = 75% to <100% wound covered &/or epithelial tissue extends >0.5cm into wound bed 3 = 50% to <75% wound covered &/or epithelial tissue extends to <0.5cm into wound bed 4 = 25% to < 50% wound covered 5 = < 25% wound covered			
	TOTAL SCORE			
	SIGNATURE			

WOUND STATUS CONTINUUM



Plot the total score on the Wound Status Continuum by putting an "X" on the line and the date beneath the line. Plot multiple scores with their dates to see-at-a-glance regeneration or degeneration of the wound.

21.5 HEALTH ECONOMIC OUTCOME MEASURES/ QUALITY OF LIFE MEASURES

Cardiff Wound Impact Schedule

Overall Quality of Life

We would like you to rate your overall quality of life during the past 7 days.

Please circle a number below

How good is your quality of life?

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

How satisfied are you with your overall quality of life?

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

Overall Comments

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Wound Healing Research Unit

University of Wales College of Medicine

Cardiff Wound Impact Questionnaire

Cardiff Wound Impact Schedule, English version for the USA

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

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

Personal Details

M F

Patient Initials **Sex**

Patient Number

Date of Birth M M D D Y Y

	1st	2nd	3rd	4th	5th
Assessment	☐	☐	☐	☐	☐

Assessment Date M M D D Y Y

Next Assessment Due M M D D Y Y

Wound(s) status Healed ☐ Not Healed ☐

Do you live on your own? Yes ☐ No ☐

How often do you see your family and friends?

Daily ☐ Once a week ☐ Less than once a month ☐

Once a month ☐

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Social Life

How <u>stressful</u> has this experience been for you during the past 7 days?

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

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Social Life

Have you <u>experienced</u> any of the following during the past 7 days?

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

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Well-being

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

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

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Physical Symptoms and Daily Living

Have you <u>experienced</u> any of the following during the past 7 days?

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

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Physical Symptoms and Daily Living

How stressful has this experience been for you during the past 7 days?

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

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21.6 ADDITIONAL INFORMATION

Not applicable.

21.7 PRINCIPAL INVESTIGATOR OBLIGATIONS (ISO 14155:2011)

1. General:
   a. The role of the PI is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.
2. Qualification of the PI. The PI shall:
   a. be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this International Standard; evidence of such qualifications of the PI and key members of the investigation site team shall be provided to the Sponsor through up-to-date Curriculum Vitae (CV) or other relevant documentation,
   b. be experienced in the field of application and trained in the use of the investigational device under consideration,
   c. disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and
   d. be knowledgeable with the method of obtaining informed consent.
3. Qualification of investigation site. The PI shall be able to demonstrate that the proposed investigation site:
   a. has the required number of eligible subjects needed within the agreed recruitment period, and
   b. has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation.
4. Communication with the IEC. The PI shall:
   a. provide the Sponsor with copies of any clinical-investigation-related communications between the PI and the IEC,
   b. comply with the requirements described in 4.5 of ISO 14155:2011:
      i. Submit to the IEC the following information, any amendments and any additional documentation required by the IEC: the Protocol; IB or equivalent; informed consent form and any other written information provided to subjects; procedures for recruiting subjects and advertising materials, if any; a copy of the CV of the PI(s) for with the IEC has oversight.
      ii. Provide documentation of the IECs approval/favorable opinion, identifying the documents and amendments on which the opinion was based, to the Sponsor, prior to commencing the clinical investigation.

iii. Submit the following to the IEC if required by national regulations, the protocol or IEC, whichever is more stringent:
   1. SAEs
   2. Requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety, and well-being, or the scientific integrity of the clinical investigation. Document and report to the Sponsor and IEC a report of deviations made to protect the rights, safety, and well-being of human subjects under emergency circumstances.
   3. Progress reports, including safety summary and deviations
   4. Amendments to any documents already approved by the IEC.
   5. If applicable, notifications of suspension or premature termination
   6. If applicable, justification and request for resuming the clinical investigation after suspension.
   7. Clinical investigation report or summary.

iv. As a minimum, during the clinical investigation, the following information shall be obtained in writing from the IEC prior to implementation:
   1. Approval/favorable opinion of amendments
   2. Approval of the request for deviations that can affect the subject's rights, safety, and well-being or scientific integrity of the clinical investigation
   3. Approval for resumption of a suspended clinical investigation if applicable.

c. obtain the written and dated approval/favorable opinion of the IEC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required,

d. promptly report any deviations from the protocol that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the IEC, protocol or national regulations. In particular circumstances, the communication with the IEC can be performed by the Sponsor, partly or in full, in which case the Sponsor shall keep the Principal Investigator informed.

5. Informed consent process. The PI shall:

a. General:
   i. Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject; except when special circumstances for emergency treatments apply (see below)

b. Process of obtaining informed consent. The general process for obtaining informed consent shall be documented in the protocol and shall comply with the following. These requirements also apply with respect to informed consent obtained from a subject's legally authorized representative:
   i. Ensure that the PI or his/her authorized designee conducts the informed consent process

ii. Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
iii. Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
iv. Not waive or appear to waive the subject's legal rights
v. Use native non-technical language that is understandable to the subject
vi. Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
vii. Include personally dated signatures and the PI or an authorized designee responsible for conducting the informed consent process
viii. Show how informed consent will be obtained in special circumstances (see below) where the subject is unable to provide him or herself, and
ix. Ensure important new information is provided to new and existing subjects throughout the clinical investigation.

c. Special circumstances for informed consent (the following provisions are subject to national regulations):
   i. Subject needing legally authorized representatives: informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g., infant, child, or juvenile, seriously ill or unconscious subject, mentally ill person, mentally handicapped person). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.
   ii. Subject unable to read or write: informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent for attesting that the information was accurately explained and that the informed consent was freely given.
   iii. Emergency treatments:
      1. For clinical investigations involving emergency treatments, when prior informed consent of the subject is not possible because of the subject's medical condition, the informed consent of the subject's legally authorized representative, if present, shall be requested.
      2. When it is not possible to obtain prior informed consent from the subject, and the subject's legally authorized representative, is not available, the subject may still be enrolled if a specific process has been described in the protocol.
      3. Arrangements shall be made to inform the subject or legally authorized representative, as soon as possible, about the subject's inclusion in the clinical investigation and about all aspects of the clinical investigation.

4. The subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows.

d. The Principal Investigator may not enroll a subject without obtaining informed consent of the subject or his/her legally authorized representative only when the following conditions are fulfilled: the prospective subject fulfils the emergency conditions and is obviously in a life-threatening situation; no sufficient clinical benefits are anticipated from the currently available treatment; there is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the investigational device is used; anticipated risks are outweighed by the potential benefits of applying the investigational device ; the legally authorized representative cannot be promptly reached and informed.

e. Information provided to the subject. All information pertinent to the clinical investigation, including at least the following, shall be provided in writing and in native, non-technical language that is understandable to the subject (or the subject's legally authorized representative):
   i. Description and purpose
   ii. Potential benefits
   iii. Risks and inconveniences or the subject and, when applicable, for any embryo, fetus or nursing infant
   iv. Alternative procedures
   v. Confidentiality
   vi. Compensation
   vii. Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation
   viii. Information on the role of Sponsor's representative in the clinical investigation
   ix. Contact persons
   x. Statement declaring that new findings or the reasons for any amendment to the protocol that affect the subject's continued participation shall be made available to the subject.
   xi. Statement indicating that, upon the subject's approval, the subject's personal physician will be informed of the subject's participation in the clinical investigation
   xii. Termination procedures

f. Informed consent signature shall contain the following:
   i. The voluntary agreement to participate in the clinical investigation and follow the investigator's instructions
   ii. A statement declaring that refusal of participation incurs no penalty for the subject
   iii. A statement declaring that discontinuation at any time incurs no penalty for the subject
   iv. A statement with regard to the possible consequences of withdrawal
   v. An acknowledgment of the information provided and confirmation that all the subject's questions were answered

vi. A statement confirming that the subject or his/her legally authorized representative agrees to the use of the subject's relevant personal data for the purpose of the clinical investigation

vii. A statement confirming that the subject or his/her legally authorized representative agrees that Sponsor's representatives, regulatory authorities and IEC representatives will be granted direct access to the subject's medical records.

g. New information: if new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing consent in writing.

h. ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent, and

i. ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

6. Compliance with the protocol. The Principal Investigator shall:

a. indicate his/her acceptance of the protocol in writing,

b. conduct the clinical investigation in compliance with the protocol,

c. create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,

d. ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the protocol and instructions for use,

e. propose to the Sponsor any appropriate modification(s) of the protocol or investigational device or of the use of the investigational device,

f. refrain from implementing any modifications to the protocol without agreement from the Sponsor, IEC and regulatory authorities, if required,

g. document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation,

h. ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,

i. ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,

j. ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports,

k. maintain the device accountability records,

l. allow and support the Sponsor to perform monitoring and auditing activities,

m. be accessible to the monitor and respond to questions during monitoring visits,

n. allow and support regulatory authorities and the IEC when performing auditing activities,

o. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and

p. review and sign the clinical investigation report, as applicable.

7. Medical care of subjects. The Principal Investigator shall

a. provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events,
b. inform the subject of the nature and possible cause of any adverse events experienced,
c. provide the subject with the necessary instructions on proper use, handling, storage, and return of the investigational device, when it is used or operated by the subject,
d. inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required,
e. provide the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed,
f. ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation,
g. if appropriate, subjects enrolled in the clinical investigation shall be provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided),
h. inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation, and
i. make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights.

8. Safety reporting. The Principal Investigator shall:
   a. record every adverse event and observed device deficiency, together with an assessment,
   b. report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the protocol,
   c. c) report to the IEC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or protocol or by the IEC,
   d. report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and
   e. supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.