Sponsor Name and Address:	T. J. Smith & Nephew Ltd., 101 Hessle Rd, Hull, HU3 2BN, UK
Investigational Product(s)	PICO 14
Protocol Author(s):	Samia Shah – Snr Clinical Study Manager Michelle Foster – Clinical Study Statistician Brian Gilchrist – Clinical Strategy Lead

1. SIGNATURES.

1.1 PRINCIPAL INVESTIGATOR SIGNATURE PAGE.

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

I have read the attached protocol entitled "A prospective, study to evaluate the safety and performance of PICO 14 in the management of acute and inclusion", version 2.0, dated 12/SEP/2021 and agree to abide by all provisions set forth herein.
I agree to comply with the Investigator's Obligations stipulated in Section 17.3 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+Nephew Ltd.

Name, Address, Professional Position	Signature	Date Signed (DD/MMM/YYYY)
MR. S. KARLAKKI CONSULTANT SURGEON RJAH INFIRMARY		26/OCTOBER/2021

1.2 COORDINATING INVESTIGATOR APPROVAL.

I have read the attached protocol entitled "A prospective, study to evaluate the safety and performance of PICO 14 in the management of acute and chronic wounds", version 2.0, dated 12/SEP/2021 and agree to abide by all provisions set forth therein.

Name, Address, Professional Position	Signature	Date Signed (DD/MMM/YYYY)
MR. SIKARCARRA CONSULTANT SURGEON RJAH, OSWESTRY		26 OCTOBER 2021

1.3 SPONSOR APPROVAL.

	Job title	DocuSign Stamp
Head of Global Clinical Operations	Senior Director Global Clinical Affairs	DocuSigned by: Rachael Winter Signer Name: Rachael Winter Signing Reason: I approve this document Signing Time: 13-Oct-2021 | 11:53:56 BST A32F12A80F1B4490986E80ACCB7471CB
Head of Global Clinical Strategy	Senior Director Global Clinical Strategies	DocuSigned by: Elizabeth Huddleston Signer Name: Elizabeth Huddleston Signing Reason: I approve this document Signing Time: 14-Oct-2021 | 12:23:51 BST C809EF989A504C77BC7277E0F8E14B1D
Head of Global Biostatistics	Senior Director Global Data Analytics	DocuSigned by: Alan Rossington Signer Name: Alan Rossington Signing Reason: I approve this document Signing Time: 13-Oct-2021 | 11:50:30 BST 556E7DBFCA8A4287A7EE3EE9B5B3ABFD
Medical Affairs Representative	Vice President, Medical Affairs	DocuSigned by: Signer Name: Luca Orlandini Signing Reason: I approve this document Signing Time: 15-Oct-2021 | 06:41:18 BST FC872951AC1C4261B85EC7A7CD09ACDC

2. SYNOPSIS.

Title of Study:	A prospective study to evaluate the safety and performance of PICO 14 in the management of acute and chronic wounds.
Study Design:	• Prospective • Multi-centre • Non-randomised
Study Type:	Prospective, non-random, non-blinded case series.
Study Product:	PICO 14.
Comparison Group(s)*: (*if applicable)	There is no comparison group in this study.
Study Purpose:	To generate evidence of the safe and effective use of the device in the management of chronic open wounds (pressure ulcers, venous leg ulcers, diabetes-related foot ulcers), dehisced surgical wounds and closed surgical incisions. The study comprises the PMCF for a new variant of an established product.
Primary Objective:	To assess the functional performance of PICO 14 through verification of delivery of negative pressure and wound exudate management.
Secondary Objective(s):	**Closed incisions ONLY :** To assess clinical performance and safety of the PICO 14 NPWT system within 30 days of surgery through: • Incidence of Surgical Site Infection (SSI) – Superficial, deep. [CDC criteria]. • Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep etc.), seroma, necrosis, hematoma, suture abscess]. • Condition of peri-wound skin assessed through visual inspection at 7, 14 and 30 days. • Patient tolerability assessed by level of pain and level of satisfaction. • Clinician acceptability assessed by ease of application and removal. • Dressing wear time, dressing change frequency and conformability will be assessed. • Scar quality measured by Patient and Observer Scar Assessment Scale (POSAS) score.

	Chronic Wounds and dehisced wound ONLY:
	To assess clinical performance and safety of the PICO 14 NPWT system within 28 days therapy period through:
	• Incidence of infection.
	• Dressing wear time, dressing change frequency and conformability will be assessed.
	• Wound assessment:
	  ○ Appearance of the wound.
	  ○ Condition of peri-wound skin.
	  ○ Level of exudate.
	  ○ Wound pain.
	  ○ Size of wound (percentage reduction in area, depth, and volume).
	• Patient tolerability assessed by level of pain and level of satisfaction.
	• Clinician acceptability assessed by ease of application and removal.

Other Objective(s):	No other objectives.
Statistical Rationale:	Data extracted from a PICO sample device showed that the mean operating pressure was -80.2mmHg (SD=14.8). It is assumed that all the PICO 14 pumps will have a similar mean operating pressure. Based on these assumptions 55 subjects are required to achieve 80% power to detect equivalence within a 6mmHg margin, at the significance level of $\alpha = 0.025$, using two one sided t-tests (TOST). It is expected that approximately 20% of the subjects may be lost to follow up by the end of the study and so to account for this 70 subjects will be recruited into the study.
Sample Size:	The study will include 70 patients. There will be a minimum of 10 of each of the following wound type; venous leg ulcers, diabetes-related foot ulcers, pressure ulcers, dehisced surgical wounds and post-operative incisions.
Number of Study Sites:	Up to ten.
Targeted Global Regions	US, Canada, UK and Europe.

Inclusion Criteria:	• The subject must provide written informed consent. • Subjects eighteen (18) years of age or older. • Willing and able to make all required study visits. • Able to follow instructions. • Subject is suitable to participate in the study in the opinion of the Investigator. **Closed Incisions ONLY:** • Subject has a suitable, closed surgical incision which the clinician considers is suitable for PICO therapy, where it is expected that the therapy will be applied for up to 14 days. • Any closed surgical incision in a patient in which the patient is deemed high risk of developing SSI in the opinion of the investigator. **Chronic wounds ONLY:** • Patients with any chronic wound* which the treating clinician deems is suitable for management with single-use disposable NPWT where it is expected that the therapy will applied for up to 28 days. *Chronic wound in this study is defined as any wound of less than three months duration that is not healing after 4 weeks of standard care and having addressed the underlying cause. **Dehisced surgical wounds ONLY:** • Patients with dehisced wounds in which the clinician believes is suitable for PICO therapy where therapy is expected to be applied for up to 28 days. *Wound dehiscence is a surgical complication in which two sides of a surgical incision separate and rupture along the incision, dehiscence typically is diagnosed after 2-3 days post-surgery and up to a month with more complicated surgeries [58]. Please note the pathway to recruiting participants with dehisced wounds has changed to widen the recruitment reach. This does mean that participants seen in the community for dehisced wound will be eligible to join study, the sites will be able to screen for participants using both pathways, whether seen in clinic by surgeon in charge or in the community.

Exclusion Criteria:	• Contraindications (per the PICO 14 IFU) or hypersensitivity to the use of the investigational product or their components (e.g. silicone adhesives and polyurethane films [direct contact with incision], acrylic adhesives [direct contact with skin], polyethylene fabrics and super-absorbent powders [polyacrylates]) within the dressing). • Subjects who require the use of SECURA non-sting barrier skin wipes and have hypersensitivity to the ingredients in the wipes. • Participation in the treatment period of another clinical trial within thirty (30) days of operative visit or during the study. • Subjects with skin features (e.g. tattoos, skin colour, pre-existing scarring) which in the opinion of the Investigator, will interfere with the study assessments. • Patients undergoing a procedure as part of palliative care (to be confirmed during surgery). • Subjects who have participated previously in this clinical trial • Subjects with a history of poor compliance with medical treatment. • Malignant wounds, open abdomen, wounds which have been previously managed with NPWT in the previous four weeks. • Pregnancy. • Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study. • Presence of infection as determined by the clinical signs and symptoms (International wound infection[59]).
Study Duration:	It is anticipated that enrolment will take 18 months.
Primary endpoint:	Functional clinical performance of the PICO 14 NPWT system over the treatment period to include: • Delivery of -80mmHg negative pressure to the wound bed over the treatment period. This will be measured by download of the built-in data chip from the PICO 14 devices to collect NPWT delivery status. • Exudate management assessed by no occurrence of exudate leaks during the treatment period resulting, or not, in an unplanned dressing change.

Secondary endpoint(s):	**Closed Incisions Only:** Clinical performance and safety of the PICO 14 NPWT system over a 14 day therapy and 30 day follow-up period to include: • Scar quality measured by POSAS score at Day 14, and day 30. • Incidence of Surgical Site Infection (SSI) and incidence of Surgical Site Complication (SSC) within 30 days of surgery [CDC criteria]. • Condition of peri-wound skin assessed through visual inspection at 7, 14 and 30 days. • Level of pain on application, during wear and at dressing removal assessed by VAS scale over the 14 day treatment period. • Patient satisfaction during wear assessed over the 14 day period. This includes leakage, feeling of moisture on the skin, odour control, level of protection, comfort and showerproof qualities. • Ease of application and removal of the PICO 14 dressing. • Dressing wear time. • Dressing conformability. • Dressing change frequency and reason for dressing change. • Clinician acceptability of PICO 14 system at discontinuation of therapy. • Patient acceptability of PICO 14 system at discontinuation of therapy. **Chronic wounds and dehisced surgical wounds only:** Clinical performance and safety of the PICO 14 NPWT system over a 28 day therapy and no follow-up period to include: • Incidence of clinical infection. • Appearance of the wound in terms of, tissue type and amount, exudate type and amount, skin condition surrounding the wound, peripheral tissue edema and induration. • Condition of peri-wound skin assessed through visual inspection at 7, 14, 21 and 28 days. • Percentage reduction in area and volume from baseline to day 7, day 14, 21 and day 28. • Level of pain on application, during wear and at dressing removal assessed by VAS scale over the 28 day treatment period. • Patient satisfaction during wear assessed over the 28 day period (for each treatment period). This includes overall performance of dressing, comfort, noise level, discreteness,

	portability, interference with daily living – showering, sleeping, socializing and working. • Ease of application and removal of the PICO 14 dressing. • Dressing wear time. • Dressing conformability • Dressing change frequency and reason for dressing change. • Clinician acceptability of PICO 14 system at discontinuation of therapy. • Patient acceptability of PICO 14 system at discontinuation of therapy.
Other endpoint(s):	No other end points.
Safety Data	Data will be collected on adverse events and device deficiencies during the study period.

2.1 STUDY SCHEDULE- CLOSED INCISIONS ONLY.

Schedule of events	Pre-Operative Data	Operative Data DAY 0	DAY 7 Visit (-3 days)	End of therapy assessment DAY 14 (-2 days)	Exit visit DAY 30 (±3 days)	Additional dressing change (Day 1-13)	Unscheduled Visit or Early Exit
Informed Consent	X						
Inclusion/Exclusion	X	X					
Demographics/ Medical History	X	X					
Incision assessment		X	X	X	X		X
Dressing assessment			X	X		X	X
Complications assessment		X	X	X	X	X	X
Photographic assessment		X	X	X	X	X	X
Operative Collection		X		X			
POSAS				X	X		
Concomitant Medication	X	X	X	X	X	X	X
Dressing application		x	x	Return to standard care		X	X
Dressing removal Assessment			X	X		X	X
Patient and clinician acceptability questionnaire completion			X	X	X		X
Discharge Data Collection, if applicable					X		
Adverse Event Assessment	X	X	X	X	X	X	X
Device Deficiency Assessment		X	X	X		X	X
End of Study/Exit					X		X

2.2 STUDY SCHEDULE- CHRONIC WOUNDS AND DEHISCED SURGICAL WOUNDS ONLY.

Schedule of events	Pre-Treatment Data	Treatment Data DAY 0	DAY 7 Visit (-3 days)	DAY 14 Visit (-2 days)	Day 21 Visit (-3 days)	End of therapy and Exit visit DAY 28 (-3 days)	Additional dressing change (Day 1-27)	Unscheduled Visit or Early Exit
Informed Consent		X						
Inclusion/Exclusion	X	X						
Demographics/ Medical History	X	X						
Wound Assessment (including measurement)		X	X	X	X	X		X
Dressing assessment			X	X	X		X	X
Complications assessment		X	X	X	X	X	X	X
Photographic assessment		X	X	X	X	X	X	X
Treatment Data Collection		X	X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X
Dressing application		X	X	X	X	Return to standard care	X	X
Dressing removal Assessment			X	X	X	X	X	X
Patient and clinician acceptability questionnaire completion			X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X
Device Deficiency Assessment		X	X	X	X		X	X
End of Study/Exit						X		X

3. STUDY CONTENTS.

3.1 TABLE OF CONTENTS.

3.2 LIST OF TABLES.

3.3 LIST OF FIGURES.

3.4 LIST OF ABBREVIATIONS AND DEFINITIONS.

Abbreviation	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
BSI	British Standards Institute
CE	Conformité Européene
CER	Clinical Evaluation Report
CRF	Case Report Form(s)
CRO	Contract Research Organization
CV	Curriculum Vitae
DD	Device Deficiency(ies)
FAS	Full Analysis Set Population
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
HIPAA	Health Information Portability Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
ISF	Investigator Site File
ITT	Intention to Treat population
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
NHS	National Health Service
PI	Principal Investigator
PMCF	Post-Market Clinical Follow

Abbreviation	Definition
PP	Per-protocol Population
RCT	Randomized Controlled Trial
S+N	T. J. Smith & Nephew Medical Ltd.
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety population
SAP	Statistical Analysis Plan
Tx	Treatment
VAS	Visual Analogue Score
USADE	Unanticipated Serious Adverse Device Effect(s)

4. INTRODUCTION

4.1 BACKGROUND

4.1.1 THE COST OF WOUND HEALING FAILURES AND COMPLICATIONS.

Facilitation of effective wound healing should be one of the primary therapeutic targets in any instance where injury to the skin tissue has occurred. Surgical procedures that result in disruption to the skin tissue include closed surgical incisions, posing its own challenges in the healing process. Skin grafting has been routinely adopted in defects that cannot be closed directly, encompassing a range of chronic[1] and acute wounds[2]. Due to the nature of grafts they have shown to be complex to heal[3], with major causes of failure being the formation of blisters or hematoma beneath the graft[3] and infection development. Closed surgical incisions involve primary closure of wounds following surgical procedures[4]. These incisions may encounter surgical site complications; however the degree of risk is likely to differ. Complications may consist of wound dehiscence, cellulitis, necrosis, superficial, deep and organ space surgical site infection, and delayed healing[5,6].

Due to their distinctive features the definition of success when treating each wound type can be reported differently within the literature, however ultimately the goal remains the same. For closed abdominal incisions and closed knee arthroplasty achievement of complete healing and avoidance of surgical site complications are common endpoints. Wound complications rates have been documented between 26-34%[6-8] and 9-12%[9-11] in closed abdominal incisions and closed knee arthroplasty respectively. A common factor that each wound type shares is the potential for failures to result in reoperation, re-hospitalisation, prolonged length of hospital stay and additional treatment resulting in increased costs[6,12,13]. In burns unit inpatients it has been shown that skin graft costs were $17,220 [14], while wound complications following laparotomy are estimated to be an additional $2,000–$3,700 [6,15]. In primary total knee arthroplasty the mean direct costs of 30 day readmissions has been shown as $13,008 and revision cases even higher at $29,893 [16].

In addition to the financial burden, failure to heal can negatively impact patient's lives affecting physical, social, emotional and economic wellbeing [6,17]. Therefore it is vital that the primary focus of wound management is to achieve full healing in a timely manner without impediment.

4.1.2 USE OF PORTABLE NEGATIVE PRESSURE IN WOUND HEALING.

Negative Pressure Wound Therapy (NPWT) was first developed in the 1990s' - with dramatic uptake since its establishment. It has been shown to be effective in the management of acute and chronic open wounds[18]. In current literature use of NPWT has demonstrated a good success rates in skin grafts3, closed abdominal incisions[19] and closed knee arthroplasty[20]. NPWT use on general surgery closed incisions has been reported to reduce surgical site complications including infection[21,22], dehiscence[23] and delayed healing[24]. This has also included some studies using single-use NPWT[25-27].

The PICO pump is a canister-free, disposable, single-use NPWT device which generates an effective nominal negative pressure of 80 mm Hg[28] and provides therapy for up to fourteen days. The PICO pump is connected to a conformable dressing which is designed to be easily applied and removed, while minimising skin trauma[29]. The device delivers negative pressure across the wound bed or closed incision[30] and surrounding area, and manages the fluid away from the wound or closed incision through a unique combination of absorbency and evaporation[28,30].

It is thought that NPWT may have numerous mechanisms of action when used to manage skin grafts and surgical incisions. Successful integration of grafts to the recipient area consists of three phases: firstly a fibrin layer forms binding the graft to the bed, secondly recipient and donor end capillaries align and finally the graft is revascularised[31]. It is thought that NPWT could facilitate this process through increased local blood flow, closer proximity of graft to wound bed, removing seromas and hematomas from under the graft, reducing bacterial load and preventing shearing of the graft[32]. Sposato et al (2001)[33] supported this understanding reporting that NPWT draws secretions through a vacuum-sealed dressing, preventing accumulation of fluid underneath the graft. In surgical incisions the main mechanisms of action involve reducing oedema, stimulating perfusion, and managing exudate. Post-operative oedema in the peri-wound tissue is thought to limit tissue perfusion and high levels of wound fluid loss have been correlated with increased risk

of post-operative infection and dehiscence[34]. Xia et al (2014)[35] demonstrated that in 20 patients with infected wounds NPWT significantly increased blood flow in the wounds when compared to pre application levels. In a study by Young et al (2012)[36] four patients with pressure ulcers had oedema and wound bed thickness assessed during follow-up. They demonstrated a rapid reduction of periwound tissue oedema over four days and a 20% increase in thickness of wound bed by day seven of therapy.

Ultimately use of NPWT for skin grafts, closed surgical incisions will be judged on its ability to increase healing success rates while minimising risk of complications. To enable it to achieve this it must be amenable with patients and healthcare practitioner's requirements and so ensure compliance with the required negative pressure protocol.

A summary of known and potential risks and benefits to humans of the Investigational Product (IP) can be found in the Package Insert/Instructions for Use of PICO 14.

4.2 LITERATURE SUMMARY.

For each of the wound types a literature search was conducted to identify studies involving NPWT with particular focus on single-use portable systems where possible. Key studies relating to each area have been described below.
Application as a post-operative dressing for surgically closed incisions is a relatively new use of NPWT; however despite this it has still received reasonable attention within the literature.

In 2019, NICE (UK) released a guidance document recommending the use of PICO[38] on closed surgical incisions (in high-risk patients), following an assessment of the clinical evidence for the device against standard of care. It is also worth noting that a Medtech Innovation Briefing released by NICE (UK) also exists for PREVENA[37], however, this document does not make any recommendations on the value or benefits of using PREVENA on closed surgical incisions.

In the case of PICO [37], a meta-analysis was performed on 31 studies, 15 of which were RCTs and 16 non-randomised comparative observational studies. The study design for the RCTs was based on the prevention of SSCs in closed surgical incisions at high risk of complications post-operation in 5 different surgical specialties: orthopaedic, colorectal, obstetric, plastic and cardiothoracic. Pooled effect estimates from a random-effects meta-analysis of the 8 studies showed a significant reduction in surgical site infection rates in favour of PICO dressings (n=1,804, odds ratio [OR] 0.51, 95% confidence interval [CI] 0.3 to 0.82; p=0.006). Of the 16 non-randomised comparative observational studies, 10 compared the rates of SSI using PICO dressings with standard wound dressings in people with closed surgical incisions. The studies included 6 different types of surgery (orthopaedic, colorectal, obstetric, plastic, cardiothoracic and vascular). Pooled effect estimates from a random-effects meta-analysis of the 10 studies showed a significant reduction in SSI in favour of PICO dressings (n=2,669, OR 0.27, 95% CI 0.14 to 0.53; p=0.001). However, these observational studies may have overestimate the clinical benefits of PICO dressings because of potential selection and publication bias.

From these 31 studies, NICE found that reductions in SSI with PICO varied across different types of surgery: it was only significantly reduced by PICO in obstetric surgery and orthopaedic surgery. However, the rate of seroma was reduced in 2 RCTs and 5 observational studies in a range of surgical specialties (n=771, OR 0.19, 95% CI 0.08 to 0.47; p=0.0003). In terms of adverse effects, NICE pointed out that PICO may be linked to increased risk of skin blisters. One RCT reported a higher overall rate of blisters in people who had PICO compared with those who had standard wound dressings (11% versus 1%). The rates of blisters varied considerably between the 3 surgeons who conducted the study.

The main conclusions of the NICE guidance were: 1) it supports the use of PICO NPWT for closed surgical incisions in the NHS (UK) based on the association of fewer surgical site infections and seromas with these devices compared with standard wound dressings; 2) PICO should be considered as an option for closed surgical incisions in people who are at high risk of developing

surgical site infections; 3) PICO was judged to provide extra clinical benefits at a similar overall cost compared with standard wound dressings.

A recent randomised controlled trial[38] compared the postoperative surgical site infection in closed laparotomy wounds treated with either PICO or standard dressings. In the 50 patients (25 per cohort) it was shown that incidence of surgical site infection at 30 days postoperatively was significantly reduced within the group treated with PICO (8.3% NPWT; 32.0% control, p = 0.043). This advantage of treatment with PICO was also reflected in a significant reduction in the length of hospital stay (6.1 days NPWT; 14.7 days control, p = 0.019). In Pellino et al's [27] prospective study (2014), also using PICO, they assessed similar outcomes of surgical site events and compared results to a cohort using conventional dressings. Patients enrolled in the study included those undergoing primary wound closure following breast or colorectal surgery. In the equally divided 50 patient colorectal surgery cohort, PICO resulted in significantly fewer instances of surgical site events (2 NPWT; 11 control, p = 0.008). It also resulted in nearly half the length of hospital stay compared to patients treated with conventional dressings (7.1 days NPWT; 12 days control, p = 0.001). These findings have been further confirmed through a meta-analysis subgroup comparing PICO to standard care in abdominal surgery[26].

In revision hip and knee surgery Cooper and Bas (2016)[39] have previously compared the outcomes of closed incision NPWT and sterile antimicrobial dressing. In this 138 patient (30 NPWT; 108 antimicrobial dressing) retrospective study they found the NPWT cohort developed significantly fewer overall wound complications (6.7% NPWT; 26.9% antimicrobial dressing, p = 0.024). Total surgical site infections were also shown to be lessened (3.3% NPWT; 18.5% antimicrobial dressing, p = 0.045). Furthermore, trends highlighted a lower number of superficial wound dehiscence and reoperations in the NPWT group; however these findings were non-significant. Karlakki et al (2016)[20] came to a similar conclusion when they evaluated the use of PICO in patients undergoing elective primary total hip and knee arthroplasties. Within this non-blinded randomised control trial 220 patients were recruited and assigned to be treated with either incisional NPWT or conventional dressings. Their findings revealed that NPWT resulted in a non-significant lower number of surgical wound complications when compared to the conventional dressing group (2.0% NPWT; 8.4%

control, p = 0.06) and a shorter hospital stay (3.8 days NPWT; 4.7 days control, p = 0.07). Further studies have suggested the same trend in reduced wound complication when PICO is applied to hip and knee revision arthroplasties[40], however this is not unanimously agreed upon for all NPWT systems[41].

Finally, in their study Hudson et al (2015)[34] brought all these wound types together in a prospective, open label, non-comparative study. They assessed the functionality and performance of PICO in 20 patients with closed surgical wounds (including knee implants and abdominal), traumatic wounds or meshed split thickness skin grafts. Results showed within 14 days 55% of wounds had closed with a further 40% progressing to closure. In three case examples this study also demonstrated the ability for, the then prototype, PICO system to achieve near continuous negative pressure within therapy limits. Provided as a convenient, all-in-one, canister-free system, the current PICO versions support patients in maintaining their daily activities. Patients may be safely discharged with PICO in place[28,29,42]. The size and simplicity gives patients' confidence that they can manage the system at home.

Surgical wounds at risk or surgical wounds with surgical site complications (SSC).

This study will focus on closed surgical wounds in patients at risk of a surgical site complication (SSC) that may cause the healing process to stall (become sub-acute), or lead to poor tissue repair, excessive scarring and/or other adverse outcomes. The main risk factors associated with developing SSCs[37] are shown below in **Table 4.2-1.**

Patient-related	Surgery-related
Age >65 years	Wound classification
Diabetes	Site and complexity of the procedure
Obesity	Repeat operations
Cigarette smoking	Emergency operations
Underlying illness e.g. COPD, renal insufficiency	
Nutritional status	
Radiation or chemotherapy exposure	

Compromised immunity, such as high dose steroid therapy	

Risk factors for surgical site infection

Table 4.2-1 Describing characteristics in a patient with risk factors that can lead to higher risk of SSI.

The most common wound-site complications are dehiscence, haematoma, seroma and surgical site infections (SSIs) (**Figure 4.2-1**, below). These are often interconnected, potentially serious complications can result in delayed or poor quality healing. Dehiscence, when a wound bursts open, can have multiple causes such as overtight closure of the wound edges, over use of the wound area leading to failure of the closure method and infection. Haematoma is a complication involving a collection of blood and fluid beneath the suture line/wound closure, which may force the wound to open up/dehisce. Seromas, common after breast mastectomy and some other types of surgery, are pockets of clear serous fluid that may persist until resorbed by the body. Sometimes, calcified tissue forms.

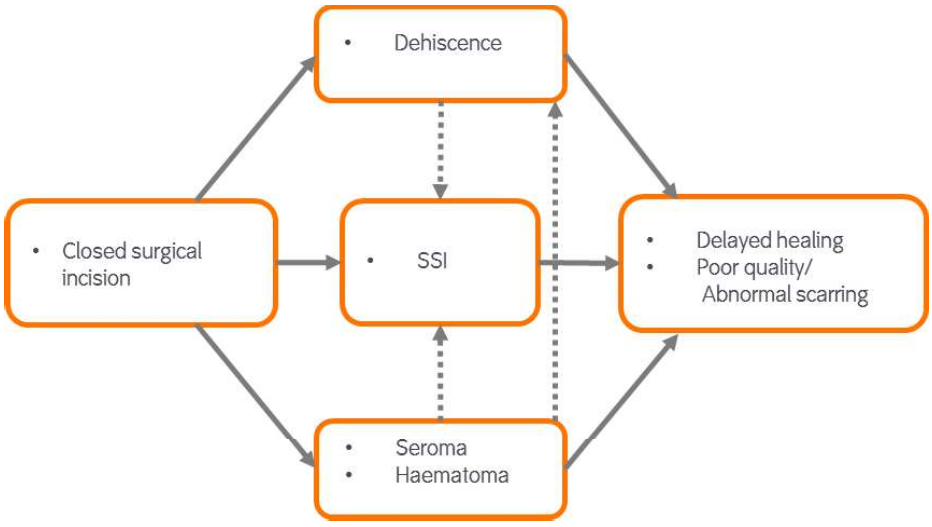


Figure 4.2-1: Relationships between surgical site complications

In respect of SSIs, the important clinical features are peri-incisional erythema, serous or purulent exudate and superficial dehiscence, which may be accompanied by systemic signs[43]. They can

be classified as superficial incisional, deep incisional or organ/space infections and are applicable to all types of surgery[44]. For a small number of patients, SSI may progress beyond a superficial wound infection to a deep incisional or organ/space infection and affect grafts and prostheses.

PICO use in chronic wounds.

Chronic wounds are defined as wounds which are characterised by either delayed healing (typically more than 6-12 weeks) or by wounds which do not heal at all. In the US alone, an estimated 4.5 million people have chronic wounds108. Wounds can become chronic for a number of reasons; often they are stalled in the inflammatory stage of the healing process and the presence of elevated levels of matrix metallo-proteases (MMPs) as an underlying cause of wound chronicity has recently been identified.

Although commonly grouped together, chronic wounds are more correctly defined and treated according to their underlying aetiology.

Negative Pressure Wound Therapy (NPWT) in its modern form first appeared in mainstream clinical medicine with the publication of two back to back articles in Annals of Plastic Surgery in 1997 [12,13]. The first article examined the mechanisms of action of NPWT using pigs and the second article described the clinical effects of NPWT on a wide range of acute, sub-acute and chronic wounds. Simply stated, NPWT consists of inserting a filler such as a polyurethane foam into a wound; covering the wound and filler with a film dressing and applying suction (negative pressure) to the enclosed cavity. In essence, the clinician had converted an open wound into a closed wound and the application of suction removes wound exudates which are conventionally collected in a canister connected in series with the suction.

NPWT is often referred to as vacuum assisted closure or “VAC” (although this is actually a brand name owned by a manufacturer, Kinetic Concepts Inc. KCI); topical negative pressure (TPN); or sub atmospheric pressure. In this review NPWT will be used throughout as this term has being adopted by clinicians and all manufacturers as a generic term for this type of treatment.

NPWT has quickly been established as a fundamental clinical tool for treating a wide range of wounds that pose the most difficult challenges in both adults and paediatric patients. For example, Argenta & Morykwas13 reported their experiences in 300 wounds of which 296 responded favourably. The wounds consisted of 175 chronic wounds, which by definition have proved to be

slow to heal; 94 sub-acute wounds such surgical incisions that have dehisced and now represent a significant and unexpected burden on the clinician and patient; and 31 acute wounds such as traumatic injuries which also responded well to NPWT. Such wounds could be dressed with relatively simple absorbent or occlusive dressings, whereas NPWT typically requires the additional expense and inconvenience of suction (often a heavy electrical pump) and a canister to collect the wound exudate. Clearly the difficulties presented by the application of NPWT provide significant beneficial effects so as to offset its disadvantages. Antony & Terrazas 200414 described early experiences of NPWT treated patients where persistent wound infections in 42 sternal, spinal and lower extremity wounds were treated with antimicrobials and NPWT for a mean duration of 29.3 days with all wounds eventually closing by around 8 weeks. This illustrates a fundamental principle of NPWT. NPWT is very often used to regain control of the wound; to kick start the healing process and progress the wound along a healing trajectory so that conventional wound therapy can be resumed with greater effect. Until recently, NPWT was seldom used all the way through second intention closure.

Wada *et al* 200615 treated difficult to heal complex lower extremity wounds, sacral pressure ulcers and traumatic wounds with NPWT for a period of only 8 days after which surgical procedures (skin grafts or flaps) were used to close the wounds successfully. The preparation of the wound bed and the use of NPWT to improve the efficacy of subsequent surgical procedures is another clear characteristic of the way NPWT is deployed. The use of NPWT on specific clinical indications will be covered in greater detail below. NPWT has also been successfully applied to a wide range of wounds in paediatric and neonatal patients16-18.

Chronic wounds in Literature are well supported with a total of 318 patients reported. Five comparative studies (Dowsett et al, 2017[45], Schwartz et al, 2015[46], Kirsner et al, 2019[47], CIME/021[48] and Wang et al, 2017[49]) found significant decreases in wound size when compared to comparators. Most other studies saw healing or reductions in wound size.

The total number of patients with ulcers treated with the PICO system in published, peer-reviewed studies was 261 Adeyami & Waycaster, 2018 [16]. Commonly reported outcomes related to wound healing or wound size reduction. Patient/clinician satisfaction was also measured in several

studies[45,46,50], with most feedback being positive. Many studies were not comparative, or did not carry out statistics and so only Dowsett et al, 2017, Schwartz et al, 2015, Kirsner et al, 2019 and Wang et al, 2017[49] found significant decrease in wound size. No studies reported significantly worse outcomes for the use of PICO on this indication.

With regards to adverse events, complications and complaints observed in the literature, no device related adverse events or complications were reported in most studies[45,49,51-56]. Hurd et al, 2014[50] reported that 7% of patients discontinued treatment due to hospitalization , 8% due to excessive exudate, and 3% on doctor's orders (unknown reason). There was one death (0.3%), and 1.5% discontinued for unknown reasons. It was also reported that device related reasons for treatment discontinuation were loss of seal in 3.1%, and poor patient compliance in 1.9%. Schwartz et al, 2015[46] reported wound infection in 16.6% of patients, and local irritation due to fixation strips in 8.3%. Kirsner et al, 2019[47] reported AEs in 3.8% that were likely to be device related, this was lower than the comparator which reported an 11% AE rate. No adverse events were observed in Menzies et al, 2017[57] although 1 patient (25%) was unable to obtain a seal due to use of PICO on the neck.

It is clear that the patient populations intended to be exposed to PICO are very wide. These various populations are comprised of relatively healthy individuals with acute traumatic wounds through to patients with acute surgical wounds and/or patients with concomitant medical disorders, such as peripheral vascular disease and/or diabetes, particularly within the context of chronic wounds. Whilst a large segment of the patient population, especially in regard to chronic wounds, may be elderly, the proposed intended uses of PICO NPWT systems do not preclude patients of any particular age or demographic. Indeed, within the context of trauma, burn wounds and/or surgical wounds, it is realistic to anticipate that the clinical use of PICO NPWT systems will extend from childhood and adolescence, into adulthood and the elderly.
Overall, based on its intended clinical use PICO 14 is considered to be clinically interchangeable for the management of chronic wounds, acute wounds, traumatic wounds, sub-acute and dehisced wounds, ulcers (such as pressure or diabetic), partial thickness burns, flaps and grafts, and surgically closed incision wounds.

Where a wound is proving difficult to heal, the typical approach is now often to try standard care (compression therapy, advanced wound dressings) first before progressing to more advanced techniques should this prove unsuccessful. Some of these advanced therapies are discussed below:

Despite analyzing 78 RCTs (7014 participants primarily women) in a Cochrane review and network systematic analysis of dressings, including silver, impregnated, and topical agents for treating VLUs, there was no certainty regarding which were most effective for healing86. In general, the studies had small numbers of patients per treatment and there was a high risk of bias.

Moues *et al* 2011129, in a systematic review of NPWT which identified more than 400 clinical papers and review articles, identified a single RCT in regard to the use of NPWT in VLUs and reported faster wound bed preparation times, faster median time to complete healing and better skin graft take rate in NPWT treated wounds. The authors noted the cost efficiency in favour of NPWT in this indication.

Dumville *et al* 2015a130 performed a systematic review in regard to the use of NPWT used within the context of leg ulcers in any care setting. For this review, the authors searched several healthcare databases for published and unpublished RCTs comparing the effects of NPWT with alternative treatments or different types of NPWT in the treatment of leg ulcers; only one 60 patient randomised study was identified. In this study population, the authors report a range of ulcer types that were venous arteriolosclerotic and venous/arterial in origin. Study participants had recalcitrant ulcers that had not healed after treatment over a six-month period. Participants allocated to NPWT received continuous negative pressure until they achieved 100% granulation (wound preparation stage). A punch skin-graft transplantation was conducted and the wound then exposed to further NPWT for four days followed by standard care. Participants allocated to the control arm received standard care with dressings and compression until 100% granulation was achieved. These participants also received a punch skin-graft transplant and then further treatment with standard care. All participants were treated as in-patients until healing occurred. The authors reported that there was low quality evidence of a difference in time to healing that favoured the NPWT group: the study reported an adjusted hazard ratio of 3.2, with 95% confidence intervals (CI) 1.7 to 6.2. The follow-up period of the study was a minimum of 12 months. There was no evidence of a difference in the total number of ulcers healed (29/30 in each

group) over the follow-up period; this finding was also low quality evidence. There was low quality evidence of a difference in time to wound preparation for surgery that favoured NPWT (hazard ratio 2.4, 95% CI 1.2 to 4.7). Limited data on adverse events were collected: these provided low quality evidence of no difference in pain scores and Euroqol (EQ-5D) scores at eight weeks after surgery.

4.3 STUDY PURPOSE.

Most previous studies have used traditional NPWT systems as part of their design. Though the technical applications of the traditional and newer single-use systems are comparable it is possible that some of the features of the latter may influence clinical outcomes. In addition to the limitations highlighted above, the cited studies have seldom assessed the ease of management and acceptability of NPWT systems. Although clinical outcomes may be considered paramount, these usability factors could also play a key role in ensuring compliance with negative pressure protocols.

This study is being conducted to evaluate the safe and effective use of the PICO 14 system in chronic wounds and surgically closed incision sites as part of the Post Market Clinical Follow Up plan for this product, for the purpose of continuing CE (Conformité Européene) Mark approval in accordance with MEDDEV 2.12-2.

The aim of this study is to assess the safety and performance of the PICO 14 system in surgically closed incisions, chronic wounds and dehisced surgical wounds.

A summary of known and potential risks and benefits to humans of each test article can be found in the Instructions for Use of PICO 14.

4.4 SAFETY CONSIDERATIONS.

The Healthcare Professional (HCP) should read the IFU for PICO 14 before use. The IFU gives full details on the contraindications and precautions to take with use of the product and include:

Contraindications:

PICO 14 is contraindicated for:

- Patients with malignancy in the wound bed or margins of the wound (except in palliative care to enhance quality of life).
- Previously confirmed and untreated osteomyelitis.
- Non-enteric and unexplored fistulas.
- Necrotic tissue with eschar present.
- Exposed arteries, veins, nerves or organs.
- Exposed anastomotic sites.

PICO 14 should not be used for the purpose of:

- Emergency airway aspiration.
- Pleural, mediastinal or chest tube drainage.
- Surgical suction.

Warnings:

- The PICO 14 pump contains a magnet. Interaction between your device and other medical devices can result in device failure and lead to serious harm, including death. For this reason the device must be kept at least 10cm away from all implantable or life sustaining medical devices. Extension tubes are included to enable the pump to be positioned more than 10cm away from any devices that could be affected. This warning applies to ALL users including patients, caregivers, healthcare professionals and all persons close to the device.

- Certain patients are at high risk of bleeding complications which, if uncontrolled, could potentially be fatal. Patients must be closely monitored for bleeding. If sudden or increased bleeding is observed, immediately disconnect pump, leave dressing in place, take appropriate measures to stop bleeding and seek immediate medical assistance.

- Haemostasis must be achieved before applying the dressing, although the use of anticoagulants does not deem a patient inappropriate for treatment with PICO 14. Patients suffering from difficult haemostasis or who are receiving anticoagulant therapy have an increased risk of bleeding. During therapy, avoid using haemostatic products that may increase the risk of bleeding, if disrupted. Frequent assessment must be maintained throughout the therapy.

- At all times care should be taken to ensure that the pump and tubing and connectors do not lie in a position where it could cause pressure damage to the patient.

- Become twisted or trapped under clothing or bandages so that the NPWT is blocked.

- The PICO 14 pump is not MRI compatible. Remove the PICO 14 pump from the dressing before entering the MRI suite.

- PICO dressings should only be applied and changed by a healthcare professional.

Precautions:

Precautions should be taken in the following types of patients who are at high risk of bleeding complications:

- Receiving anticoagulant therapy or platelet aggregation inhibitors or actively bleeding.

- Having weakened or friable blood vessels or organs in or around the wound as a result of, but not limited to; anastomoses, infection, trauma or radiation.

- Suffering from difficult wound haemostasis.
- Untreated for malnutrition.
- Non-compliant or combative.
- Suffering from wounds in close proximity to blood vessels or delicate fascia.
- PICO 14 does not contain audible alerts. The pump should be carried so that it is accessible and the patient/ healthcare professional can check the status routinely.
- Although PICO dressings can be used under clothing/bedding, it is important that occlusive materials e.g. film dressings, are not applied over the pad area of the dressing as this will impair the intended evaporation of moisture through its outer layer.
- Where PICO dressings are used on patients with fragile skin, a skin protectant such as SECURA™ No-Sting Barrier Film should be used on areas of skin where fixation strips are to be applied. Inappropriate use or repeated application of fixation strips may otherwise result in skin stripping.
- Do not use PICO dressings with oil based products such as petrolatum as it may compromise establishing an effective seal.
- PICO 14 may be used in conjunction with surgical drains provided the dressings not placed over tubing where it exits the skin. Any surgical drain should be routed under the skin away from the edge of the dressing and function independently of the PICO 14 System.
- The pump must be protected from sources of fluid e.g. from incontinence or spillages. Discontinue PICO 14 use if fluid ingress is observed.

- When showering, the PICO 14 pump should be disconnected from the dressing. Whilst disconnected, ensure the end of the tubing attached to the dressing is facing down so that water does not enter the tube.

- Do not cut the PICO dressing pad as this may lead to loss of NPWT application.

- Always ensure that the PICO dressing is positioned centrally over the wound. The soft port should be positioned uppermost on intact skin and not extend over the wound so that the risk of fluid collecting around the soft port and potentially blocking the NPWT is minimised.

- CT scans and x-ray have the potential to interfere with some electronic medical devices. Where possible, move the pump out of the x-ray or scanner range. If the pump has been taken into the CT scan or x-ray range, check that the system is functioning correctly following the procedure.

- When applying dressings next to one another, ensure the dressing borders do not overlap.

The clinician should read the IFU for PICO 14 before use. The IFU gives further details of the above points and additional information on PICO 14 contraindications and precautions.

Risks associated with use of PICO 14 within the present study will be mitigated as follows:

- Study personnel will be competent in the correct use of PICO 14 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 patient eligibility.

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

- PICO 14 will be used within its registered indication.
- PICO 14 will only applied by a healthcare professional in line with the IFU.

4.5 BENEFITS.

PICO systems maintain a nominal (-80 mmHg) negative pressure wound therapy which may promote surgical site healing via removal of low to moderate levels of exudate and infectious materials.

Potential benefits of this device include reduction of oedema, promotion of epithelialization at the surgically closed incision site, and a reduction of SSI and other SSC. And in the case of chronic wounds and dehisced surgical wounds lack of signs of infection as well as wound area reduction.

4.6 ANTICIPATED SERIOUS ADVERSE DEVICE EFFECTS.

Excessive bleeding is a serious risk associated with the application of suction to wounds which may result in death or serious injury. Careful patient selection, in view of the above stated contraindications, warnings and precautions is essential. Subjects with incisions that are actively bleeding are not eligible to participate in this study unless haemostasis has been achieved (to be confirmed during surgery). The surgical site and dressing should be monitored for any evidence of a change in the blood loss status of the subject.

4.7 OVERALL BENEFIT/RISK ANALYSIS.

The anticipated medical benefits are considered to outweigh the overall or individual residual risks associated with PICO 14 within the proposed indications. The risks associated with PICO 14 are addressed with reference to the warnings and precautions in the IFU.

5. OBJECTIVE(S).

5.1 PRIMARY OBJECTIVE.

To assess the functional clinical performance of PICO 14 NPWT system over 14 days therapy through the verification of delivery of negative pressure and wound exudate management.

5.2 SECONDARY OBJECTIVES.

Closed incisions ONLY

To assess clinical efficacy and safety of the PICO 14 NPWT system within 30 days of surgery through:

- Incidence of Surgical Site Infection (SSI) – Superficial, deep. [CDC criteria].
- Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep etc.), seroma, necrosis, hematoma, suture abscess].
- Condition of peri-wound skin assessed through visual inspection at 7, 14 and 30 days.
- Any pain experienced by the subject in relation to the PICO 14 system.
- Patient tolerability assessed by level of pain and level of satisfaction.
- Clinician acceptability assessed by ease of application and removal.
- Dressing wear time, dressing change frequency and dressing conformability.
- Scar quality measured by Patient and Observer Scar Assessment Scale (POSAS) score.

Chronic Wounds and dehisced surgical wounds ONLY

To assess clinical efficacy and safety of the PICO 14 NPWT system within 28 days therapy period through:

- Incidence of infection.
- Condition of peri-wound skin assessed through visual inspection at 7, 14, 21 and 28 days.
- Any pain experienced by the subject in relation to the PICO 14 system.

- Wound assessment:
    - Appearance of the wound.
    - Level of exudate.
    - Wound pain.
    - Size of wound (percentage reduction in area, depth, and volume).
- Patient tolerability assessed by level of pain and level of satisfaction.
- Clinician acceptability assessed by ease of application and removal.
- Dressing wear time, dressing change frequency and dressing conformability.

5.3 OTHER OBJECTIVES.

No other objectives.

5.4 SAFETY.

To assess Adverse Events and Device Deficiencies.

5.5 CLAIMS.

Data generated from the study will populate a clinical study report which will feed into the clinical evaluation report for PICO 14 to evaluate the safe and effective use of the PICO 14 system in chronic open wounds and closed surgical incisions, and support part of the PMCF plan for this product, for the purpose of continuing CE (Conformité Européene) Mark approval in accordance with MEDDEV 2.12-2.

6. INVESTIGATIONAL PRODUCTS.

6.1 IDENTIFICATION.

6.1.1 INVESTIGATIONAL PRODUCT.

PICO 14 is a single-use Negative Pressure Wound Therapy System consisting of a small portable pump, 2 AA batteries, 2 dressings and fixation strips. The PICO 14 pump maintains NPWT at 80 mmHg (nominal) to the wound surface. Exudate is managed by the dressing through a combination of absorption and evaporation of moisture through the outer film. The PICO 14 dual dressing kit is intended to be used for up to 14 days on low to moderately exuding wounds. The frequency of dressing changes can be affected by multiple factors such as wound type, wound size, rate or volume of exudate, orientation or environmental conditions. Additional dressings will be provided as required.

PICO 14 may be used in a hospital or community setting and is indicated for acute and chronic, sub-acute, dehisced and traumatic wounds, flaps and grafts, surgically closed incision sites, and partial thickness burns. For this study, PICO 14 will be used to manage post-surgical wounds closed by primary intention, chronic wounds and dehisced surgical wounds as defined in the study eligibility criteria. PICO 14 is also used on chronic wounds such as Venous Leg ulcer, Arterial Leg Ulcer and Diabetic foot Ulcer and pressure ulcers. This is due to the PICO 14 pump capability of providing therapy for 14 days. PICO 14 will be applied for 14 days **(for closed incisions only)** with a dressing change at 7 days on low exuding wounds. For moderately/high exuding wounds each PICO dressing can be used for up to 4 days.

Please note for chronic and dehisced surgical wounds PICO 14 may be applied for up to 28 days by using two PICO 14 systems for treatment.

PICO 14 is manufactured by Smith+Nephew Medical Limited, 101 Hessle Road, Hull, HU3 2BN, UK. PICO 14 is packed in the UK with individual components made in the following countries:

- Dressing – UK.
- Fixation strips – origin as marked.
- Pump – China.
- Batteries – origin as marked.

The dressing is the part of the system that is applied directly to the patient. It is a 4 layer fluid management system that includes:

- A top film layer with a high moisture vapour transmission rate allows one-way transpiration of exudate vapour.
- Proprietary absorbent layer moves exudate away from the wound and initiates evaporation.
- Airlock layer maintains open airflow and allows even distribution of negative pressure across the dressing.
- Silicone contact allows fluid to pass and minimizes pain of removal.

The dressing sizes available for this product are:

- 10 x 20 cm
- 10 x 30 cm
- 10 x 40 cm
- 15 x 15 cm
- 15 x 20 cm
- 15 x 30 cm
- 20 x 20 cm
- 25 x 25 cm
- Small Multisite
- Large Multisite

The adhesive fixation strips are polyurethane film and are used for secondary fixation around the edges of the dressing. This ensures a sufficient seal for the negative pressure to be maintained at the wound site.

During this study, a subject will receive NPWT via the use of one (1) PICO 14 pump for 14 days with additional dressing changes taking place as clinically warranted throughout these 14 days.

6.1.2 ANCILLARY PRODUCT.

SECURA No-Sting Barrier Film wipes

SECURA No-Sting Barrier Film wipes are water-based acrylate polymer-impregnated wipes, which can be used to protect the peri-wound skin prior to the application of the secondary fixation strips in subjects with more fragile skin. A supply of SECURA non-sting skin barrier wipes will be provided by S&N.

Catalogue #	Description	Units per Carton
66800712	SECURA No-Sting Barrier Film Wipe (1ml)	50 wipes

Manufacturer: Smith and Nephew Medical Limited, 101 Hessle Road, Hull, HU3 2BN, UK

RENASYS Adhesive Gel Patches

RENASYS Adhesive Gel Patches are double sided silicon adhesive hydrogel patches, which can be used to aid application in awkward areas, if required. A supply of RENASYS Adhesive Gel Patches will be provided by S&N.

Catalogue #	Description	Units per Carton
66801082	RENASYS Adhesive Gel Patches (10 x 7 cm)	10 strips

Manufacturer: Smith and Nephew Medical Limited, 101 Hessle Road, Hull, HU3 2BN, UK.

6.2 COMPARATOR TREATMENT.

No comparator products will be used in this study.

6.3 PRODUCT USE.

Sites will be requested to refer to the IFU for full guidance on how the dressings and fixation strips should be applied for PICO 14. The use of the PICO adhesive strips is mandatory for the IP per the application instructions in the IFU. All sites will be trained in and experienced in the use of PICO kits. This will be established through prior general use of PICO kits during routine medical practice at the site and through some practise use of PICO 14 if required, to minimise learning effects prior to the live phase of the study.

6.4 INVESTIGATIONAL PRODUCT – PICO 14.

Please refer to the IFU for full guidance on how the dressings and fixation strips should be applied. All sites will be trained and experienced in the use of PICO 14 kits. This will be established through prior general use of PICO 14 kits during routine medical practice at the site. Previous experience with PICO should include use on incision sites and not limited to open or chronic wounds.

6.5 LABELING OF INVESTIGATIONAL PRODUCT.

As all product supplied is commercially available and used within its approved indications there is no need for labelling.

6.6 PRODUCT ACCOUNTABILITY PROCEDURES.

The investigational site will maintain an inventory of the IP/Ancillary Products and Study Supplies.

The Sponsor or its designee will provide a log(s) to facilitate IP/Ancillary Products and Study Supplies inventory control. All IP/Ancillary Products and Study Supplies accountability logs must be retained in the Investigator Site File (ISF). These records must be available for inspection by the Sponsor, its designees, or by regulatory agencies at any time.

The Study Monitor will ensure that the procedures and records are in place for the appropriate reconciliation of all IP/Ancillary Products and Study Supplies. As part of monitoring, the Study

Monitor will check that site personnel are following the proper procedures for accountability and completing all necessary documentation.

7. SUBJECT ENROLLMENT AND WITHDRAWAL.

7.1 SUBJECT POPULATION.

Seventy patients with Chronic open wounds (pressure ulcers, venous leg ulcers, diabetes-related foot ulcers, dehisced surgical wounds) and Closed surgical incisions, will be recruited to the study and will receive therapy with PICO 14. There will be a minimum of 10 of each of the following wound type; venous leg ulcers, diabetes-related foot ulcers, pressure ulcers, dehisced surgical wounds and post-operative incisions.The patients will be recruited from up to 7 sites in the United Kingdom, EU, and US, Canada. Sites failing to enroll may be replaced.

7.2 INCLUSION CRITERIA.

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

1. The subject must provide written informed consent.
2. Subjects eighteen (18) years of age or older.
3. Willing and able to make all required study visits.
4. Able to follow instructions.

5. **Closed Incision wounds ONLY:**
   - Subject has a closed surgical incision which the clinician considers is suitable for PICO therapy, where it is expected that the therapy will be applied for a minimum of 14 days.
   - Subject has a closed surgical incision which the clinician is deemed high risk of developing SSI.

Risk factors for surgical site infection

Patient-related	Surgery-related
Age (> 65 years)	Wound classification
Diabetes	Site and complexity of the
Obesity	procedure
Cigarette smoking	Repeat operations
Underlying illness e.g. COPD, renal insufficiency	Emergency operations
Nutritional status	
Radiation or chemotherapy exposure	
Compromised immunity, such as high dose steroid therapy	

Chronic wounds ONLY:

- Patients with any chronic wound* which the treating clinician deems is suitable for management with single-use disposable NPWT where it is expected that the therapy will applied for a minimum of 28 days.

*Chronic wound in this study is defined as any wound of less than three months duration that is not healing after 4 weeks of standard care and having addressed the underlying cause.

Dehisced surgical wounds ONLY:

- Patients with dehisced wounds in which the clinician believes is suitable for PICO therapy where therapy is expected to be applied for up to 28 days.

*Wound dehiscence is a surgical complication in which two sides of a surgical incision separate and rupture along the incision, dehiscence typically is diagnosed after 2-3 days post- surgery and up to a month with more complicated surgeries [58].

Please note the pathway to recruiting participants with dehisced wounds has changed to widen the recruitment reach. This does mean that participants seen in the community for dehisced wound will be eligible to join the study, the sites will be able to screen for participants using both pathways, whether seen in clinic by surgeon in charge or in the community.

7.3 EXLUSION CRITERIA

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

1. Contraindications (per the PICO 14 IFU) or hypersensitivity to the use of the investigational product or their components (e.g. silicone adhesives and polyurethane films [direct contact with incision], acrylic adhesives [direct contact with skin], polyethylene fabrics and super-absorbent powders [polyacrylates]) within the dressing).

2. Subjects with extremely fragile skin who require the use of SECURA non-sting barrier skin wipes and have hypersensitivity to the ingredients in the wipes.

3. Participation in the treatment period of another clinical trial within thirty (30) days of operative visit or during the study.

4. Subjects with skin features (e.g. tattoos, skin colour, pre-existing scarring) which in the opinion of the Investigator, will interfere with the study assessments.

5. Patients undergoing a procedure as part of palliative care.

6. Subjects who have participated previously in this clinical trial and who have healed or been withdrawn.
7. Subjects with a history of poor compliance with medical treatment.

8. Malignant wounds, open abdomen wounds which have been previously managed with NPWT in the previous four weeks.

10. Women who are pregnant, nursing, or of child-bearing potential who are not utilizing highly effective birth control measures

11. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

12. Presence of infection as determined by the clinical signs and symptoms (International wound infection[59]).

* Please see table below for clinical symptoms of infection as determined by the International Consensus update 2016

Local infection		Spreading infection[22, 23]	Systemic infection[22, 23]
Covert (subtle) signs of local infection:[2, 27-36] ■ Hypergranulation (excessive 'vascular' tissue) ■ Bleeding, friable granulation ■ Epithelial bridging and pocketing in granulation tissue ■ Wound breakdown and enlargement ■ Delayed wound healing beyond expectations ■ New or increasing pain ■ Increasing malodour	Overt (classic) signs of local infection:[2, 27, 28, 35, 36] ■ Erythema ■ Local warmth ■ Swelling ■ Purulent discharge ■ Delayed wound healing beyond expectations ■ New or increasing pain ■ Increasing malodour	■ Extending in duration +/- erythema ■ Lymphangitis ■ Crepitus ■ Wound breakdown/ dehiscence with or without satellite lesions ■ Malaise/ lethargy or non-specific general deterioration ■ Loss of appetite ■ Inflammation, swelling of lymph glands	■ Severe sepsis ■ Septic shock ■ Organ failure ■ Death

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.

Part of the screening process will include documentation of women's childbearing potential. If the woman is not of childbearing potential this should be documented in the medical history (e.g., surgically postmenopausal, postmenopausal [i.e., at least one year without menses]). For women of childbearing potential, their method of birth control should be documented in the source.

A screen failure is any subject who has signed a consent form and goes on to become ineligible for the study prior to the application of the study dressing (section 7.8.1 and 7.8.2). Information must be captured in the appropriate CRFs up to the point of screen failure with the reason for screen failure specified. Screen failures will be documented in the subject's source documents and on the Trial Register. Any screen failures will be replaced.

7.5 INFORMED CONSENT.

Before conducting any study procedures or examinations, the purpose and nature of the study will be explained to the subject in their native language. The subject, or their legally authorized representative, will then **read, sign, and personally date the IRB/IEC approved informed consent document(s)** (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent documentation will be provided to the subject, a copy will be placed in the subject's medical record, with the original filed in the ISF.

If the subject is unable to read, the informed consent document and associated study information may be read aloud to the subject in the presence of an impartial witness. If possible the subject shall sign and personally date the Informed Consent Form (ICF). Where this is not possible, due to difficulties in writing, the subject shall provide verbal consent to participate in the study. The

witness shall then personally sign and date the informed consent form, attesting that the information was accurately explained and that the informed consent was freely given.

All subjects will be given time to consider participation following the explanation of the study/reading of the patient information sheet. At least 24 hours will be needed before patient can consent to study. . No true emergency cases (where the subject is unconscious or does not have time to consider the study) will be consented for this study.

If the subject is unable to read, the informed consent document and associated study information may be read aloud to the subject in the presence of an impartial witness. If possible, the subject shall sign and personally date the Informed Consent Form (ICF). Where this is not possible, due to difficulties in writing, the subject shall provide verbal consent to participate in the study. The witness shall then personally sign and date the informed consent form, attesting that the information was accurately explained and that the informed consent was freely given.

Due to COVID-19 pandemic verbal consenting might be required by sites to achieve consent from participants who are unable to attend at the time of consent. Process for this will involve, site to provide PIS and full information on the study at least 24 hours prior to the Verbal call and consent.

Verbal consent will be sought and the consenter will date and sign the ICF on the participant behalf, the participant will be screened thereafter and once in clinic they will be asked to sign and date the ICF personally. In the case of emergency situations, the ICF may be obtained and information on the clinical study may be given after the decision to include the subject in the clinical investigation if the following situations apply:

- Subject is unable to consent due to the form of wound (dehished wound only) in which wound becomes opened and dehishced and requires urgent treatment within hours of the wound being diagnosed as such by Investigator. Due to the time sensitivity of this cohort of participants, the risk is that this cohort might not be included in study if emergency consenting is not allowed.

ICF will be obtained from the legally designated representative as soon as possible. In addition, informed consent to continue participation in the clinical investigation will be obtained from the subject as soon as the subject is capable to give informed consent.

If the subject or the legally designated representative (if applicable) does not give consent, the subject or legally designated representative will be informed of the right to object to the use of data obtained from the clinical investigation.

If new information becomes available during the course of the study that can significantly affect a subject's future health and medical care, Smith + Nephew will ensure that information shall be provided to the subject(s) affected in written form and if relevant, all affected subjects shall be asked to confirm their continuing consent in writing.

7.6 ENROLLMENT.

Enrolment in this study shall occur at the point the consent process has been completed and study number is allocated to the subject.

7.7 LOST TO FOLLOW-UP.

A subject will be considered lost to follow-up if he/she does not appear for the scheduled study visit for 2 consecutive visits and does not return for a final visit, and study personnel are unable to contact the subject.

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 OF TREATMENT.

Subjects may be withdrawn early from study treatment for the following reasons:

- Subject does not return following treatment (and pump is lost).
- Treatment is prematurely ended for any reason (i.e. due to removal of the system by the subject, failure of the pump, dressing falls off, seal can no longer be established).
- Treatment is disrupted for longer than 24 hours (i.e. airtight seal was disrupted and was not re-established with a 24 hour time period).
- At the discretion of the Investigator due to:
    - A change in treatment is clinically warranted (to include further treatment following 14 day therapy)/28 day therapy for chronic wounds and dehisced surgical wounds.
    - An adverse event or device deficiency.
    - Any other significant reason identified by the Investigator.

7.8.2 WITHDRAWAL FROM STUDY.

The Investigator may withdraw subjects from the study for many reasons, including but not limited to the following:

- subject noncompliance (e.g., did not follow instructions, took disallowed medications)
- subject lost to follow-up
- if the Investigator or the Sponsor stops the study for any reason and decides to withdraw subject(s) from the study
- concurrent illness

- Adverse Events/Adverse Device Effects
- any other significant reason identified by the Investigator

For each case, information will be obtained in the source document and the Case Report Form (CRF), detailing circumstances leading to the withdrawal.

Subjects who are treated for with surgery that ends with a closed incision and subjects who drop out, or are withdrawn, will not be re-entered into the study at a later date.

7.8.3 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.

7.8.4 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 study is a prospective, multi-centre, non-randomised, non-blinded, single arm follow-up study to assess performance, safety and efficacy of PICO 14. It is anticipated that up to 7 sites will participate within Canada, UK and EU.

The treatment phase will be 14 days post-surgery with a 30 days study follow-up period/ up to 28 days therapy period for chronic wounds and dehisced surgical wounds with no follow up. Fourteen days of therapy has been chosen as the length of time to assess device efficacy with use in real

clinical conditions, since this is the length of time one system will operate and previous studies involving incisions suggest that benefit is generally achieved over 7-10 days of NPWT therapy.

Figure 8.1-1: Study Flowchart – Schedule of PICO 14 therapy comparison and follow up for assessment of surgical site complications- Closed Incision only

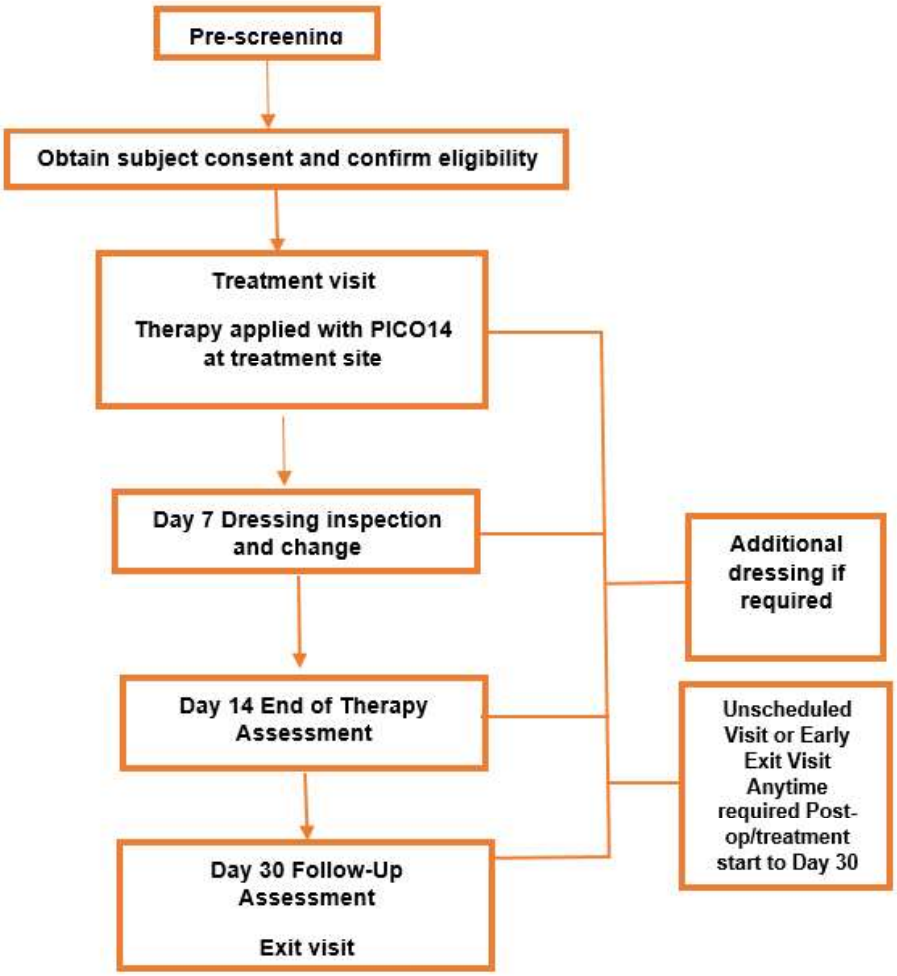
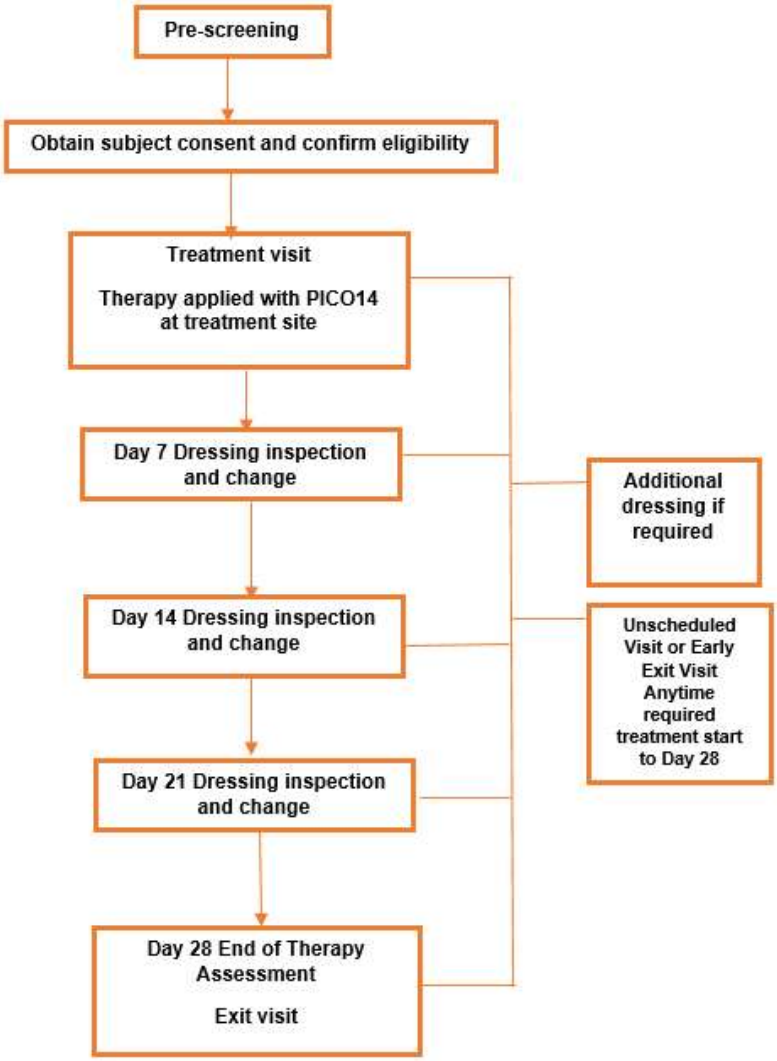


Figure 8.1-2: Study Flowchart – Schedule of PICO 14 therapy comparison and follow up for assessment of reference wound- Chronic wound and dehisced surgical wounds only



8.2 ALLOCATION AND BLINDING

8.2.1 Treatment Allocation

This study is not randomized.

8.2.2 Blinding

This study is non-blinded.

8.3 DATA MANAGEMENT

This study utilizes a validated, 21 CFR Part 11 compliant, electronic data capture system. Access to the electronic data capture system is controlled through Smith and Nephew procedures.

A Data Management Plan (DMP) is written according to Smith and Nephew procedures containing details of the data management process. The following is a brief description of the key points detailed in this plan.

8.4 DATA REVIEW AND QUALITY ASSURANCE

Data will be transcribed from the data source to an electronic Case Report Form (eCRF). All data requested on the eCRFs are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The Principal Investigator must provide his/her electronic signature on the appropriate eCRFs to be documented in compliance with local regulations. Changes to data previously submitted to the sponsor will require a new signature by the Investigator to acknowledge/approve the changes.

Visual and computer data review will be performed in line with Smith and Nephew procedures to identify possible data discrepancies. Manual and automatic queries will be created within the electronic data capture system, and will be issued by Smith and Nephew to the site for appropriate response. Site staff are responsible for resolving all queries in the electronic data capture system.

8.5 RETENTION PERIOD

All eCRFs will be archived once the study is completed and will kept for a period of no less than five years after the later of the following dates: the date of which the study is terminated or completed or; the date that the records are no longer required supporting marketing applications.

8.6 STUDY ENDPOINTS.

8.6.1 PRIMARY ENDPOINT.

Functional clinical performance of the PICO 14 NPWT system over the treatment period to include:

- Delivery of -80mmHg negative pressure to the wound bed over the treatment period. This will be measured by download of the built-in data chip from the PICO 14 devices to collect NPWT delivery status.
- Exudate management assessed by no occurrence of exudate leaks during the treatment period resulting, or not, in an unplanned dressing change.

8.6.2 SECONDARY ENDPOINTS.

Closed Incisions Only:

Clinical performance and safety of the PICO 14 NPWT system over a 14 day therapy and 30 day follow-up period to include:

- Scar quality measured by POSAS score at Day 14, and day 30.
- Incidence of Surgical Site Infection (SSI) and incidence of Surgical Site Complication (SSC) within 30 days of surgery [CDC criteria].
- Condition of peri-wound skin assessed through visual inspection at 7, 14 and 30 days.
- Level of pain on application, during wear and at dressing removal assessed by VAS scale over the 14 day treatment period.
- Patient satisfaction during wear assessed over the 14 day period. This includes leakage, feeling of moisture on the skin, odour control, level of protection, comfort and showerproof qualities.
- Ease of application and removal of the PICO 14 dressing.

- Dressing wear time.
- Dressing conformability
- Dressing change frequency and reason for dressing change.
- Clinician acceptability of PICO 14 system at discontinuation of therapy.
- Patient acceptability of PICO 14 system at discontinuation of therapy.

Chronic wounds and dehisced surgical wounds only:

Clinical performance and safety of the PICO 14 NPWT system over a 28 day therapy and no follow-up period to include:

- Incidence of clinical infection
- Appearance of the wound in terms of, tissue type and amount, exudate type and amount, skin condition surrounding the wound, peripheral tissue edema and induration,
- Condition of peri-wound skin assessed through visual inspection at 7, 14, 21 and 28 days.
- Percentage reduction in area and volume from baseline to day 7, day 14, 21 and day 28.
- Level of pain on application, during wear and at dressing removal assessed by VAS scale over the 28 day treatment period.
- Patient satisfaction during wear assessed over the 28 day period (for each treatment period). This includes overall performance of dressing, comfort, noise level, discreteness, portability, interference with daily living – showering, sleeping, socializing and working.
- Ease of application and removal of the PICO 14 dressing.
- Dressing wear time.
- Dressing conformability
- Dressing change frequency and reason for dressing change.
- Clinician acceptability of PICO 14 system at discontinuation of therapy.
- Patient acceptability of PICO 14 system at discontinuation of therapy.

8.6.3 OTHER ENDPOINTS.

- No other endpoints.
-

8.6.4 SAFETY ENDPOINTS.

Data will be collected on adverse events and device deficiencies during the study period.

8.7 METHODS USED TO MINIMIZE BIAS AND MAXIMIZE VALIDITY.

8.7.1 REDUCTION OF BIAS TOWARDS ACCEPTABILITY OF IP SYSTEM WHEN COMPARED WITH OTHER MANUFACTURERS/MODELS

Smith+Nephew will ensure that reduction of bias towards acceptability of the PICO 14 system against any others marketed, by being fully transparent with the aim of the study prior to commencing and through publishing the result of the primary endpoint following reporting on www.clinicaltrials.gov and any other applicable trial registries.

9. STUDY PROCEDURES - CLOSED INCISIONS ONLY.

9.1 VISITS AND EXAMINATIONS.

Summary

For a summary of the required procedures by visit, refer to the Study Schematic Table 13.1-1: Study Procedures by Visit.

Table 9.1-1: Study Procedures by Visit- Closed Incisions ONLY.

Schedule of events	Pre-Operative Data	Operative Data DAY 0	DAY 7 Visit (-3 days)	End of therapy assessment DAY 14 (-2 days)	Exit visit DAY 30 (±3 days)	Additional dressing change (Day 1-13)	Unscheduled Visit or Early Exit
Informed Consent	X						
Inclusion/Exclusion	X	X					
Demographics/ Medical History	X	X					
Incision assessment		X	X	X	X		X
Dressing assessment			X	X		X	X
Complications assessment		X	X	X	X	X	X
Photographic assessment		X	X	X	X	X	X
Operative Collection		X		X			
POSAS				X	X		
Concomitant Medication	X	X	X	X	X	X	X
Dressing application		X	X	Return to standard care		X	X
Dressing removal Assessment			X	X		X	X
Patient and clinician acceptability questionnaire completion			X	X	X		X
Discharge Data Collection, if applicable					X		
Adverse Event Assessment	X	X	X	X	X	X	X
Device Deficiency Assessment		X	X	X		X	X
End of Study/Exit					X		X

9.1.1 SCREENING/PREOPERATIVE VISIT (MAY BE UP TO 4 WEEKS PRIOR TO VISIT).

NOTE: Any subject who signs an informed consent/assent but fails to meet the required entry criteria is considered to be a Screen Failure. Screen Failure subjects will be assigned subject numbers and ONLY the screening visit and their demographic information must be captured in the appropriate CRF with the reason for screen failure specified.

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

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

2. Obtain demographic information and medical history, including information on all concomitant medications/therapies.
3. Screen the subject for protocol inclusion/exclusion criteria.
4. Subjects will be instructed to return to the treatment facility for the Operation Visit (within 4 weeks of consent).

9.1.2 BASELINE OPERATIVE VISIT (WITHIN 4 WEEKS OF SCREENING) - CLOSED INCISIONS ONLY.

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	Commence operation and collect surgery data [e.g. Type of surgery (closed surgical incision, (type of abdominal surgery / type of knee surgery, method of closure), and reference wound type.
3.	Collect surgery risk factors (elective/emergency surgery, laparoscopic (y/n), incision length, use of prophylactic antibiotics, type (single / double / triple agent) and when administered (prior to start of surgery/after surgery began), shaving of incision (yes / no / not needed), use of a wound protector (yes / no), clean/contaminated surgery (clean/clean-contaminated/contaminated/dirty), intraoperative warming (yes / no)).
4.	Confirm eligibility following surgery details. Assign a study number to the subject (XX.YYY where XX = site number and YYY =subject number at the site).
5.	Assess the incision characteristics for likelihood of SSC (oedema, seroma, haematoma, skin necrosis).
6.	Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated).
7.	Photograph incision using the camera provided by the Sponsor showing the photo label as supplied.
8.	Dispense study product. Record pump lot number, size of dressing used and any ancillary products applied (SECURA No-Sting Skin prep, RENASYS Adhesive Gel Patch).
9.	Assess ease of application, ease of establishing seal/negative pressure delivery, satisfaction of applying IP.
10.	Take photograph of dressing in place.
11.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse events and device deficiencies.

9.1.3 DAY 7 (-3 DAYS) FOLLOW UP DRESSING INSPECTION

1. Record date and treatment setting. If outpatient, record date of previous discharge.
2. If therapy is being discontinued prior to 7 days or dressing is no longer in place, complete the End of Therapy Assessment (9.1.6 below).
3. Record if therapy has been interrupted since the previous assessment and how long.
4. Record the use of concomitant medications.
5. Take photograph of dressing in place.
6. Assess subject comfort (yes, no) and pain level (Visual Analogue Scale).
7. If dressing change is required then please follow additional dressing study procedures.
8. If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse events and device deficiencies.
9. Instruct the subject on follow-up procedures, including returning to the treatment facility for the End of Therapy Assessment Visit at 14 (-2) days post-surgery.

9.1.4 END OF THERAPY ASSESSMENT DAY 14 (-2) DAYS.

1. Record date and treatment setting. If outpatient, and not previously recorded, record date of previous discharge.
2. If therapy is being discontinued prior to 14 days, record reason (e.g. PICO 14 NPWT system removed, treatment interrupted for 48 hours or more, clinician recommends a change in treatment, at the discretion of the Investigator, adverse event, subjects own request, lost to follow-up, other). If pump is faulty change is permissible during therapy period record the reason under Device deficiency CRF form.
3. Record the use of concomitant medications.

4. Record reason if dressing is no longer in place (e.g. pain/discomfort from the dressing, patient removed, patient's request, adverse event, no vacuum, pump turned off, reason for dressing change and exudate management data collection, other).
5. Take photograph of dressing in place.
6. Record if therapy has been interrupted since the previous assessment and how long.
7. Assess subject satisfaction (overall performance of dressing, comfort, noise level, discreteness, portability, interference with daily living – showering, sleeping, socialising, working).
8. Remove NPWT system as per procedure (section 9.2.4).
9. Assess ease of removal.
10. Record pain score (VAS) and patient comfort since last assessment and pain score on dressing removal.
11. A suitably qualified individual (as described in section 9.2.1) to complete assessment of incision. If any complications have occurred, details of this and additional procedures to be collected (9.1.9).
12. Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated).
13. Photograph the incision using the camera supplied by the Sponsor.
14. If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse events and device deficiencies.
15. Follow procedure for removal, appropriate labelling and storage of pump for return to S&N.
16. Assess clinician acceptability of PICO NPWT system (Overall satisfaction, satisfaction with ability to manage incision/, satisfaction regarding dressing retention, satisfaction as compared to other NPWT devices).
17. Complete POSAS at this visit.

9.1.5 EXIT VISIT 30 (±3) DAYS- CLOSED INCISIONS ONLY.

1. A suitably qualified individual (as described in section 9.2.1) to complete assessment of incision complications. If any complications have occurred, details of this and further to be collected (as per 9.1.10).
2. Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated).
3. Photograph wound using camera provided by Sponsor.
4. If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse events and device deficiencies.
5. Complete Exit Visit CRF and complete POSAS.

9.1.6 ADDITIONAL DRESSING CHANGE ASSESSMENT (DAY 1-13) - CLOSED INCISIONS ONLY.

PICO 14 is intended to be used for up to 14 days. Additional dressing change assessments will be completed if the dressing needs changing prior to Day 14 post surgery.

1. Record date and treatment setting. If outpatient, and not previously recorded, record date of previous discharge.
2. Record reason for dressing change (e.g. routine, dressing saturated (exudate), strikethrough, leakage, pain, loss of vacuum, dressing got wet during shower/bathing, inspection prior to patient discharge, patient removed dressing, patient's request, other).
3. Record the use of concomitant medications.
4. Record reason if dressing is no longer in place (e.g. pain/discomfort from the dressing, patient removed, patient's request, adverse event, no vacuum, pump turned off, other).
5. Record if therapy has been interrupted since the previous assessment and how long.
6. Take photograph of dressing in place.
7. Assess subject satisfaction (overall performance of dressing, comfort, noise level, discreteness, portability, interference with daily living – showering, sleeping, socialising, working).

8. Remove NPWT system as per procedure (section 9.3) for data chip collection.
9. Assess ease of removal.
10 Record pain score (VAS) since last assessment and on dressing removal.
11 A suitably qualified individual (as described in section 9.2.1) to complete assessment of wound complications. If any complications have occurred, details of this and additional procedures to be collected (per section 9.1.10).
12 Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated).
13 Photograph the incision/ using the camera supplied by the Sponsor.
14 Dispense study product. Record pump lot number, size of dressing used and any ancillary products applied (SECURA No-Sting Skin prep, RENASYS Adhesive Gel Patch).
15 Assess ease of application, ease of establishing seal/negative pressure delivery, satisfaction of applying IP.
16 Take photograph of dressing in place.
17 If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse events and device deficiencies.
18 Instruct the subject on follow-up procedures, including returning to the treatment facility for the next scheduled assessment.

9.1.7 UNSCHEDULED - SSC ASSESSMENT.

Unscheduled examinations may be conducted at the discretion of the Investigator with all obtained information recorded in the source documents and on the appropriate CRF. An unscheduled visit will be a visit that is not within the visit window for baseline, day 7 follow up and end of therapy assessment, visits. If an unscheduled visit occurs within 14 days post-start of treatment a new PICO 14 dressing may be applied to the incision if clinically warranted.

All information obtained during an unscheduled visit should be recorded in the source documents and on the appropriate CRF.

1. Record the date that the complication occurred.
2. Record the complication type (e.g. superficial infection i.e. cellulitis, deep infection, organ/space infection, oedematous, seroma, haematoma, abscess, discharge (serous exudate with inflammation, seropurulent, haemopurulent, pus), delayed healing, discoloration, unexpected pain/tenderness/bridging of the epithelium or soft tissue, abnormal smell, wound breakdown, severe bruising, superficial dehiscence, deep dehiscence, other).
3. Record procedure (e.g. opening of wound, drainage of wound infection, antibiotics—oral, antibiotics—intravenous, re-suture of wound, evacuation of hematoma, seroma aspiration, incision of an abscess, wound toilet, negative pressure wound dressing—cavity, change to antimicrobial or antibacterial treatment, other) / treatment changed to treatment changed to (e.g. a different NPWT system, simple foam dressing, antimicrobial dressing, other).
4. Record any concomitant medications.
5. The complication and any device deficiencies must be recorded as instructed in Section 12 - Adverse events and device deficiencies.

9.1.8 CONCOMITANT MEDICATIONS AND THERAPIES.

A concomitant medication (e.g. drug, substance) and a concomitant therapy (e.g. physical therapy, TENS Unit, massage) are recorded at any time from enrolment into the study through the subject's last study visit, including ongoing medications.

9.1.8.1 CONCOMITANT MEDICATIONS.

9.1.8.1.1 EXCLUDED CONCOMITANT MEDICATIONS.

The following concomitant medications are not permitted from the time of entry into the study until the exit visit has taken place:

- No other ointments/gels/topical lotions/creams should be used with the PICO system as per the IFU (other than the SECURA skin barrier wipes and RENASYS Adhesive Gel Patches provided as ancillary for the study).

9.1.8.1.2 RECORDING CONCOMITANT MEDICATIONS IN THE CRF.

All medications will be recorded in the CRF. Refer to the CRF Completion Guidelines for how medications are recorded.

9.1.8.1.3 THERAPIES PROHIBITED DURING THE STUDY.

The use of the following concomitant therapies is not permitted during the study period:

- No dressings (i.e. foam, gauze, ACTICOAT) should be used under the IP during therapy. Please note it is acceptable to use foam or gauze fillers.
- No other NPWT devices (i.e. RENASYS, Vac) should be used following the 7 day therapy treatment period unless it becomes necessary on clinical grounds and this would be the routine clinical protocol provided by the site.

9.1.8.2 RECORDING CONCOMITANT THERAPIES IN THE CRF.

Only therapies related to (directly treating) the reference incision will be recorded on the CRF. Refer to the CRF Completion Guidelines for how concomitant therapies are recorded.

9.1.9 DISCONTINUED SUBJECTS.

Discontinued subjects are those who voluntarily discontinue participation or who are lost to follow-up refer to section 5.8 for further details. Where possible, a full Exit Visit should be completed for all subjects who discontinue the study early. Where consent is withdrawn, the date and any reason given for discontinuation should be captured, at a minimum (see Section 5.8.2).

Finally, if appropriate, the Investigator will also advise the subject of subsequent therapy and/or procedures necessary for their medical condition.

Subjects who are withdrawn only from treatment will not automatically discontinue participation in the study, see Section 5.8.

9.1.10 SUBJECT PREGNANCY.

Women of child-bearing potential are 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 subject will be withdrawn from study. Pregnancy is not 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 INCISION CLOSURE AND CDC INCISION ASSESSMENT.

A medically qualified individual who is not deemed to have a vested interest in low reporting of complications and infections at an institutional level will complete incision assessment. This will include i) an assessment of whether the incision is fully closed/epithelialised an assessment of delayed healing, iii) an assessment of infection, dehiscence or other complications.

Incision closure is defined as skin closure (100% closed) without drainage or dressing requirements. Primary or first intention healing occurs when tissue is cleanly incised and re-approximated and healing occurs without complications. Incisional wounds are usually completely sealed in 24-48 hours, with continued healing of the underlying structures within 5-7 days. Delayed wound healing would be defined as an incision that is not closed, or “parts” unhealed, >7 days.

Assessment of incision infection will be completed as specified per the CDC definitions of nosocomial surgical site infections at each of the specified time points to identify whether there is superficial, deep, or organ/space infection at the incision site. Infection is defined as “the presence of one or more of the following criteria; abscess, cellulites, discharge, (serous exudate with inflammation, seropurulent, haemopurulent, pus) delayed healing, discoloration, unexpected pain/tenderness/bridging of the epithelium or soft tissue, abnormal smell, or wound breakdown”. This can occur with or without the signs of leukocytosis and fever”. Cutting K F et al. [24], (2004).

If dehiscence has occurred, the level of dehiscence will be defined as superficial (involve only separation at skin level) or deep (involve separation of tissues below the skin, may or may not include skin separation).

A training session will be held for the individuals at each site to standardise how the assessments of complication, infection and dehiscence are made.

Surgery details to be collected include the following questions:

- Date of surgical procedure (DD/MMM/YYYY).
- Collect surgery data [e.g. Type of surgery (closed surgical incision, (type of abdominal surgery / type of knee surgery, method of closure), and reference wound type and anatomical site).
- Collect surgery risk factors (elective/emergency surgery, laparoscopic (y/n), incision length, use of prophylactic antibiotics, type (single / double / triple agent) and when administered (prior to start of surgery/after surgery began), shaving of incision (yes / no / not needed), use of a incision drape (yes / no), clean/contaminated surgery (clean/clean-contaminated/contaminated/dirty), intraoperative warming (yes / no)).

To be collected for each incision:

- Closure method (sutures / staples / surgical glue / adhesive strips / other).
- Types of sutures used (nylon / polypropylene / vicryl / monocryl / other).
- Suture closure technique (simple interrupted stitch / horizontal mattress / vertical mattress / figure 8 / continuous locking / sub-cuticular / other).
- Have any drains been used (Yes / No. If Yes, number of drains used, level of exudate contained in drain (ml)).
- Duration of surgery (mins).

Incision information to be collected include the following questions.

To be completed for each incision:

Questions asked at surgery visit only

- Measure of length/size of incision (cm) – (horizontal / vertical / NA).
- Incision Characteristics – (Normal / Oedematous / Seroma / Hematoma / Dehiscence/ Skin Necrosis / Other).

Questions asked at all assessments except the surgery visit

- Level of exudate (none / light / moderate / heavy).
- Colour of exudate (serous / serosanguinous /sanguineous / tan / purulent /other).
- Level of post-surgical swelling (none / slight / moderate / severe).
- Level of bruising (none / light / moderate / severe / extreme-critical).
- Bruising site (other-please specify).
- Condition of surrounding skin (Healthy / Fragile / Inflamed / Erythematous / Oedematous / Eczematous / Macerated / Bruising / Dry & Flaky / other).
- Incision closed (healed)? (Yes / No).
    - If no:
        - Incision dehisced (Yes / No. If yes, superficial / deep / partial / length (cm)).
        - Length/parts unhealed, estimation of length/parts unhealed (cm) – (vertical/horizontal).
        - Incision clinically infected (Yes / No. If yes, deep or superficial infection).
- Clinical signs of infection (none / increased exudate-secretion levels / increased pain / increased temperature around the incision / tissue necrosis / local erythema / oedema / purulent drainage / dehiscence / odour / other).
- Assessment of incision complications (None / Superficial Infection (i.e. Cellulitis) / Deep Infection / Organ/Space Infection / Oedematous / Seroma/ Haematoma / Abscess / Skin Necrosis Partial Dehiscence / Total Dehiscence/ Superficial Dehiscence / Deep Dehiscence / Suture Abscess or Extrusions / Delayed Healing / Discolouration / Unexpected pain/tenderness/Abnormal smell / Wound breakdown / Other).
- Additional procedures performed (None / Debridement / Removal of Sutures (or clips) / Opening of incision / Drainage of incision infection / Antibiotics – Oral / Antibiotics – Intravenous / Re-suture of incision / I / Evacuation of hematoma / Seroma Aspiration / Incision of an Abscess / Debridement / Treatment changed

/ Other. If treatment changed, A different NPWT system / Absorbent dressing / Antimicrobial dressing / other).

- Incision relief (normal / flat / raised).
- Incision colour (pale / white / pink / red / purple / mix).
- Level of itching from the incision (none / slight / moderate / severe).

Question asked at assessments from Treatment Discontinuation to Day 30 for each incision

- List any dressings that have been applied to the incision since the previous assessment (None / Steri-strips / Foam dressing / Films/polymer dressing / Alginate/Hydrofiber/ Antimicrobial dressings (silver/iodine) / Hydrocolloid / Non-adherent dressing / Odour absorbent dressing / Absorbent pads / Bandages / Hydrogels / Gauze / Other).

9.2.2 ASSESSMENT OF PERI-WOUND SKIN.

The surrounding skin will also be assessed by the above mentioned clinician. The clinician whether the skin appears healthy or is fragile, inflamed, eczematous, dry/flaky, macerated or has erythema, bruising.

9.2.3 SURGICAL SITE AND DRESSING PHOTOGRAPHS.

An image of the subject's postsurgical incision will be captured prior to initial dressing application, at 7 days post operatively (or when dressing is removed) and at end of therapy at 14 days and 30 days postoperatively (or early exit visit) using a digital camera supplied by S&N. The images will be used as a pictorial record of the study reference incisions.

A photo ruler labelled with the subject's number, study number and the date will be supplied by S&N and will be placed in the field of the photograph. The image should be framed such that the entire incision/dressing nearly fills the frame. Ensure that identifying information, such as the subject's face, are not visible in the photograph. After obtaining the image, ensure that the image is clear (in focus) and that there is sufficient light to clearly see the incision/dressing. Instructions for capturing images will be supplied with the cameras. Training on the use of the camera will be given during the site initiation visit.

An image of the dressing in place will be taken after application, and before removal, to check the device compliance.

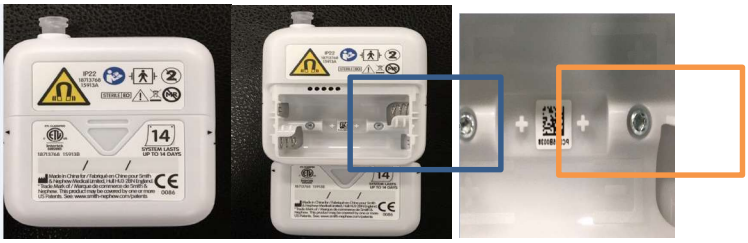
If an AE or any other change to the subject's surgical site occurs during the study, further images of the wound will be captured to document the event if there is visible impact of the AE or other change. A photograph should also be taken where appropriate of all DevD reported.

All photographs should be uploaded to the relevant assessment on the CRF.

9.2.4 DRESSING APPLICATION ASSESSMENT.

Dressing Application information to be collected include the following questions.

To be completed for each incision (Day 0 – Treatment Discontinuation):

- Any products applied at dressing application (None/ SECURA No-Sting Barrier Film wipes / RENASYS Adhesive Gel Patch / topical antibiotics / other). Reduce bioburden, Lower risk of infection, other.
    - Renasys gel patch used (Yes/No).
        - If used how long did the patch last for, and any problems upon removal.
        - Did the Renasys gel patch provide comfort to the subject's incision wound.
- PICO 14 **UDI Number** 
- PICO 14 pump Lot Number and Catalogue number will also be collected.
- If Dressing used is separate to what is provided in the PICO14 kit please record UDI, Lot and Catalogue number of the dressing.
- Size of PICO 14 NPWT dressing kit size used (10 x 20 cm / 10 x 30 cm / 10 x 40 cm / 15 x 15 cm / 15 x 20 cm / 15 x 30 cm / 20 x 20 cm / 25 x 25 cm / Small Multisite / Large Multisite).
        - Was the dressing used on the closed incision wound conformable (Yes/No)

If No, please comment.

- Easy to create a vacuum on the PICO dressing (Yes / No).
- Easy to operate the pump on the PICO dressing (Yes / No).
- Dressing application on incision:
    - Dressing easy to apply (Yes / No).
    - Satisfaction with the application of the PICO dressing (Yes / No).
    - Dressing comfortable (Yes / No) (not on day of surgery)

Question asked at all assessments from Treatment Discontinuation to Day 30 for each incision

- List the dressings that has been applied to the incision at this assessment (None / Steri-Strips / Foam dressing / Films/polymer dressing / Alginate/Hydrofiber / Antimicrobial dressings (silver/iodine) / Hydrocolloid / Non-adherent dressing / Odour absorbent dressing / Absorbent pads / Bandages / Hydrogels / Gauze / Other).

9.2.5 DRESSING REMOVAL ASSESSMENT (AT DAY 14, ALSO APPLICABLE IF DRESSING HAS TO BE CHANGED BEFORE DAY 14).

Dressing removal information to be collected include the following questions:

To be completed for each incision:

- Subject treatment setting (In-patient / Out-patient /other).
- Subject discharged from hospital since the last assessment (Yes / No / NA. If yes, date of discharge).
- Has the subject been re-admitted to hospital since the last assessment as a result of their surgery (Yes / No. If yes, date of re-admission).
- Additional procedures carried out (Yes / No. If yes, please provide details).
- Dressing comfortable during wear (Yes / No. If no, please comment).
- Dressing acceptable to the patient (Yes / No. If no, please explain).

- Acceptable dressing exudate management (Yes / No. If no, please comment).
- Level of pain from the incision since the last assessment (0-10 scale).
- Reason for dressing change (Routine/ inadequate exudate management / pain-discomfort from the dressing / dressing damaged / dressing fell off / patient removed dressing / adverse event / surgical procedure / safety alarm / dressing components not in place / no vacuum /other).
- Is the dressing still covering the incision as applied? (Yes / No).
- How long has the dressing not covered the incision? (Day / Hour / Min) if applicable.
- Has the dressing been removed at any point since application? (Yes / No).
- How long was the dressing not in place? (Day / Hour / Min).
- Has there been any period that the vacuum was not applied during therapy apart from showering? (Yes / No. If yes, for how long).
- Level of Pain on removal of dressing (0 -10 scale).
- Was the dressing easy to remove? (Yes / No. If no, please comment).

9.2.6 TREATMENT DISCONTINUATION.

Treatment discontinuation information to be collected include the following questions:

- Date of treatment discontinuation.
- Reason for treatment discontinuation (End of treatment period (14 days) / Vacuum interrupted for > 48 hours / A change in treatment is clinically warranted / Subject withdrawn—Adverse Event / Other (specify). If Incision management complete.
- Overall subject assessment of PICO 14:
    - How was the pump carried around (Pump Clip / Pocket / Hand / Other? If other, please state). If the Pump Clip used, was the clip a useful feature (Yes/No. If No, why).
    - Subject satisfaction with the following aspects of the NPWT system: Overall performance, Comfort during wear, Noise Level, Discreetness, Portability (Scale).

- Interference with daily living – Showering, Sleeping, Socialising, Working (Yes, please comment/ No)

- Overall investigator assessment of PICO 14:
  - Overall is the Investigator satisfied with the performance of the PICO 14 system (pump and dressing) (Yes / No. If No please comment).
  - Following questions will be asked :"Are you satisfied with the PICO 14 systems ability to manage wound/ incision?", Are you satisfied with the PICO 14 systems ability regarding dressing retention?" and "Are you satisfied with the PICO 14 systems ability when compared to other NPWT devices?"

9.2.7 SUBJECT EXIT.

Subject exit information to be collected include the following questions,

- Date of Subject Exit.
- Reason for Subject Exit (End of Follow Up period (30 days) / Subject Withdrawn – Non-compliance / Subject Withdrawn – Adverse Event / Subject Withdrawn – Subject's own request / Subject Withdrawn – Lost to follow-up / Investigator Decision / Other (Specify)).
- Complete of POSAS and exit questionnaire.

9.3 PICO 14 DEVICE RETURN.

All PICO 14 pumps will be returned to S&N for download of the in-built data chip. Once the pumps have been removed from the subject they are to be decontaminated using the following procedure:

- Label a zip-locked bag with subject ID number, initials and date labelled.
- At the Treatment Discontinuation Assessment the PICO dressing will be removed from the subject in order to inspect the surgical site as per the study protocol.
- The PICO dressing will be disconnected from the pump and the dressing disposed of as clinical waste.
- The surface of the pump should be wiped with a disinfectant wipe. Remove and retain the batteries. Clean the batteries and the inside of the battery compartment with a disinfectant wipe.

- Put the PICO pump and the batteries in the labelled bag.
- During the monitoring visits, the study monitor will count the devices and verify that they have been labelled correctly, collect devices and shipment will be arranged to Smith+Nephew Wound Management, Hull, UK.

In an identified handling area at Smith+Nephew Wound Management, Hull, UK, the devices shall be processed to have their internal memory contents downloaded, analysed and saved following an approved NPD (New Product Development) Work Instruction.

9.4 HEALTH ECONOMICS/QUALITY OF LIFE.

No Quality of Life Questionnaires will be collected for this study however, assessment of acceptability of the therapy will be made by specific targeted questions to the clinician and subject as described in section 9.2.5 above.

9.5 SCAR QUALITY ASSESSMENT (AT DAY 0, DAY 14 AND AT EXIT VISIT).

The Patient and Observer Scar Assessment Scale (POSAS) is a comprehensive scale that is designed for the evaluation of all types of scars by professionals and patients. The POSAS aims to measure scar quality. The Patient Scale gives the POSAS an important extra dimension because the patient's opinion is mandatory for a complete scar evaluation. The Observer Scale will be completed by an independent member of the study team.

The POSAS consists of two parts: a Patient Scale and an Observer Scale. Both scales contain six items that are scored numerically and make up a 'Total Score' of the Patient and Observer Scale. The sum altogether will give the 'Total Score' of the POSAS. Besides the 10-step scale, category boxes are available to score nominal parameters (e.g. type of colour). Moreover, the patient and observer also score their 'Overall Opinion'.

Each item of both scales has a 10-point score, with 10 indicating the worst imaginable scar or sensation. The lowest score is '1', and corresponds to the situation of normal skin (normal pigmentation, no itching etc.), and goes up to the worst imaginable. The Total Score of both scales can be simply calculated by summing up the scores of each of the six items. The Total Score will therefore range from 6 to 60. Besides the six items the 'Overall Opinion' of the scar quality is scored separately of both patients and observers.

A full description of the Patient and Observer Scar Assessment Scale can be found in appendix 22.5.

10. STUDY PROCEDURES- CHRONIC WOUNDS AND DEHISCHED SURGICAL WOUNDS ONLY.

10.1 VISITS AND EXAMINATIONS.

10.1.1 SUMMARY.

For a summary of the required procedures by visit, refer to the Study Schematic Table 10.1-1: Study Procedures by Visit.

Table 10.1-1: Study Procedures by Visit- Chronic wounds and dehisced surgical wounds ONLY.

Schedule of events	Pre-Treatment Data	Treatment Data DAY 0	DAY 7 Visit (-3 days)	DAY 14 Visit (-2 days)	Day 21 Visit (-3 days)	End of therapy and Exit visit DAY 28 (-3 days)	Additional dressing change (Day 1-27)	Unscheduled Visit or Early Exit
Informed Consent		X						
Inclusion/Exclusion	X	X						
Demographics/ Medical History	X	X						
Wound Assessment (including measurement)		X	X	X	X	X		X
Dressing assessment			X	X	X		X	X
Complications assessment		X	X	X	X	X	X	X
Photographic assessment		X	X	X	X	X	X	X
Treatment Data Collection		X	X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X
Dressing application		X	X	X	X	Return to standard care	X	X
Dressing removal Assessment			X	X	X	X	X	X
Patient and clinician acceptability questionnaire completion			X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X
Device Deficiency Assessment		X	X	X	X		X	X
End of Study/Exit						X		X

10.1.2 SCREENING VISIT/BASELINE VISIT.

NOTE: Any subject who signs an informed consent/assent but fails to meet the required entry criteria is considered to be a Screen Failure. Screen Failure subjects will be assigned subject numbers and ONLY the screening visit and their demographic information must be captured in the appropriate CRF with the reason for screen failure specified.

1. Obtain written informed consent from the subject as detailed in Section 7.5.
   ----- Do not proceed until consent has been obtained -----
2. Obtain demographic information and medical history, including information on all concomitant medications/therapies.
3. Screen the subject against eligibility criteria and assign a study number to the subject (XX.YYY where XX= site number and YYY= subject number at site.
4. Instruct the subject on treatment procedures.
5. Complete a full wound assessment sections (10.4.2).
6. Take a photograph of the reference wound showing the photo label as supplied.
7. Product/therapy used prior to study.
8. Assess the peri-wound skin.
9. Take a photograph of the reference wound showing the photo label as supplied (section 10.4.3).
10. Dispense study product. Record pump lot number, size of dressing used and any ancillary products applied (SECURA No-Sting Skin prep, RENASYS Adhesive Gel Patch).
11. Take photograph of dressing in place by camera supplied by Sponsor and add label supplied.
12. VAS score will be recorded upon product application.
13. Assess ease of application, ease of establishing seal/negative pressure delivery, satisfaction of applying IP.

14. If any AE or DevD are observed or reported, they must be recorded as instructed in Section 12, Adverse Events and Device Deficiencies. Take a photograph of the wound/dressing as appropriate.
15. Instruct subject of the follow up visit at day 7 (-3 days).

10.1.3 DAY 7 (-3 DAYS) FOLLOW UP DRESSING INSPECTION.

1. Record date and treatment setting.
2. If therapy has been discontinued prior to this visit or dressing is no longer in place, complete the End of Therapy Assessment (10.1.5below).
3. Record if therapy has been interrupted since the previous assessment and how long.
4. Record any changes in general health and record the use of concomitant medications.
5. Take photograph of dressing in place by camera supplied by Sponsor and add label supplied.
6. Dressing removal assessment.
7. Assess the peri-wound skin.
8. Complete a full Wound Assessment (section 10.4.2).
9. Take photograph of the wound site area.
10. A new dressing will be applied and the PICO14 pump will be restarted to apply for up to 7 days.
11. Take photograph of new dressing in place.
12. Assess subject comfort (yes, no) and pain level (Visual Analogue Scale).
13. If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse events and device deficiencies. Take a photograph of the wound/dressing as appropriate.
14. Instruct the subject on follow-up procedures, including returning to the treatment facility for the Assessment Visit at 14 (-2) days. Record date of assessment.

10.1.4 ASSESSMENT VISIT DAY 14 (-2) DAYS.

1. Record date and treatment setting.
2. If therapy is being discontinued prior to 14 days, record reason (e.g. PICO 14 NPWT system removed, treatment interrupted for 48 hours or more, clinician recommends a change in treatment, at the discretion of the Investigator, adverse event, subjects own request, lost to follow-up, other).
3. Record reason if dressing is no longer in place (e.g. pain/discomfort from the dressing, patient removed, patient's request, adverse event, no vacuum, pump turned off, exudate management level, other).
4. Take photograph of dressing in place.
5. If any AE or DevD are observed or reported, they must be recorded as instructed in Section 12, Adverse Events and Device Deficiencies. Take a photograph of the wound/dressing as appropriate.
6. Record any changes in general health and the use of concomitant medications.
7. Record if therapy has been interrupted since the previous assessment and how long.
8. Complete the Dressing Removal Assessment.
9. Complete a full Wound Assessment (section 10.4.2).
10. Assess the peri-wound skin.
11. Assess subject satisfaction (overall performance of dressing, comfort, noise level, discreteness, portability, interference with daily living – showering, sleeping, socialising, working).
12. Assess clinician and participant acceptability of PICO NPWT system (Overall satisfaction, satisfaction with ability to manage, satisfaction regarding dressing retention, satisfaction as compared to other NPWT devices).Record date of assessment.
13. Remove NPWT system and re-apply new PICO 14 device onto same wound.
14. Assess ease of removal.

15. Record pain score (VAS) and patient comfort since last assessment and pain score on dressing removal.
16. Photograph wound area using the camera supplied by the Sponsor.
17. Follow procedure for removal, appropriate labelling and storage of pump for return to S&N.
18. Dispense study product. Record pump batch number, size of dressing used and any ancillary products applied (SECURA No-Sting Skin prep, RENASYS Adhesive Gel Patch).
19. Take photograph of the new dressing in place.
20. Assess ease of application of new dressing.
21. Instruct the subject on follow-up procedures, including returning to the treatment facility for the Assessment Visit at 21 (-2) days. Record date of assessment.

10.1.5 DAY 21 (-3 DAYS) FOLLOWUP DRESSING INSPECTION

1. Record date and treatment setting.
2. If therapy is being discontinued prior to 21 days or dressing is no longer in place, complete the End of Therapy Assessment (10.1.5 below).
3. Record if therapy has been interrupted since the previous assessment and how long.
4. Record any changes in general health and record the use of concomitant medications.
5. Take photograph of dressing in place by camera supplied by Sponsor and add label supplied.
6. Dressing removal assessment will be performed at this visit as it is required to remove dressing at 21 days.
7. Assess the peri-wound skin.
8. Complete a full Wound Assessment (section 10.4.2).
9. Take photographs of wound area site.
10. A new dressing will be applied and the PICO 14 pump will be restarted to apply for up to 7 days.

11.	Take photograph of new dressing in place.
12.	Assess subject comfort (yes, no) and pain level (Visual Analogue Scale).
13.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse events and device deficiencies. Take a photograph of the wound/dressing as appropriate.
14.	Instruct the subject on follow-up procedures, including returning to the treatment facility for the End of therapy and Exit visit 28 (-2) days. Record date of assessment.

10.1.6 END OF THERAPY AND EXIT VISIT 28 (-3) DAYS.

1.	Record date and treatment setting.
2.	Record any changes in general health and the use of concomitant medications.
3.	Record if therapy has been interrupted since the previous assessment and how long.
4.	Take photograph of dressing in place and complete the Dressing Removal Assessment.
5.	Complete a full Wound Assessment (section 10.4.2).
6.	Assess the peri-wound skin.
7.	Assess subject satisfaction (overall performance of dressing, comfort, noise level, discretene portability, interference with daily living – showering, sleeping, socialising, working).
10.	Assess clinician and participant acceptability of PICO NPWT system (Overall satisfacti satisfaction with ability to manage, satisfaction regarding dressing retention, satisfaction compared to other NPWT devices).Record date of assessment.
11.	Remove NPWT system as per procedure 9.4 for data chip collection.
12.	Record pain score (VAS) and patient comfort since last assessment and pain score on dress removal.
13	Follow procedure for removal, appropriate labelling and storage of pump for return to S&N.
14.	Take photographs of the wound using camera provided by Sponsor (section 10.4.3) If any adverse events are observed or reported, they must be recorded as

instructed in Section 12.

15. Follow procedure for removal, appropriate labelling and storage of pump for return to S&N.
16. Complete an Exit Form and exit the subject from the study stating the date and reason discontinuation. Standard care will be provided to the subject.

10.1.7 ADDITIONAL DRESSING CHANGE ASSESSMENT (DAY 1-27).

PICO 14 dressings are intended to be used for up to 7 days. Additional dressing change assessments will be completed if the dressing needs changing prior to Day 28 therapy period.

1. Record date and treatment setting.
2. Record reason for dressing change (e.g. routine, dressing saturated (exudate), strikethrough, leakage, pain, loss of vacuum, dressing got wet during shower/bathing, patient removed dressing, patient's request, other).
3. Record the use of concomitant medications.
4. Record reason if dressing is no longer in place (e.g. pain/discomfort from the dressing, patient removed, patient's request, adverse event, no vacuum, pump turned off, other).
5. Record if therapy has been interrupted since the previous assessment and how long.
6. Take photograph of dressing in place.
7. Assess subject satisfaction (overall performance of dressing, comfort, noise level, discreteness, portability, interference with daily living – showering, sleeping, socialising, working).
8. Assess ease of removal.
9. Record pain score (VAS) since last assessment and on dressing removal.
10. A suitably qualified individual to complete assessment of wound complications. If any complications have occurred, details of this and additional procedures to be collected.
11. Assess the peri-wound skin.
12. Photograph the wound using the camera supplied by the Sponsor.

13 Dispense study product. Record pump lot number, size of dressing used and any ancillary products applied (SECURA No-Sting Skin prep, RENASYS Adhesive Gel Patch).

14 Assess ease of application, ease of establishing seal/negative pressure delivery, satisfaction of applying IP and VAS score on dressing application.

15 Take photograph of dressing in place.

16 If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse events and device deficiencies.

17 Instruct the subject on follow-up procedures, including returning to the treatment facility for the next scheduled assessment

10.1.8 CONCOMITANT MEDICATIONS AND THERAPIES.

A concomitant medication (e.g. drug, substance) and a concomitant therapy (e.g. physical therapy, TENS Unit, massage) are recorded at any time from enrolment into the study through the subject's last study visit, including ongoing medications.

10.1.8.1 CONCOMITANT MEDICATIONS.

10.1.8.1.1 Excluded Concomitant Medications

The following concomitant medications are not permitted from the time of entry into the study until the exit visit has taken place:

- No other ointments/gels/topical lotions/creams should be used with the PICO system as per the IFU (other than the SECURA skin barrier wipes and RENASYS Adhesive Gel Patches provided as ancillary for the study).

10.1.8.1.2 Recording Concomitant Medications in the CRF

All medications will be recorded in the CRF. Refer to the CRF Completion Guidelines for how medications are recorded.

10.1.8.1.3 Therapies Prohibited During the Study

The use of the following concomitant therapies is not permitted during the study period:

- No dressings (i.e foam, gauze, ACTICOAT) should be used under the IP during therapy. Please note it is acceptable to use foam or gauze fillers.
- No other NPWT devices (i.e RENASYS, Vac) should be used following the 7 day therapy treatment period unless it becomes necessary on clinical grounds and this would be the routine clinical protocol provided by the site.

10.1.8.1.4 Recording Concomitant Therapies in the CRF

Only therapies related to (directly treating) the reference incision will be recorded on the CRF. Refer to the CRF Completion Guidelines for how concomitant therapies are recorded.

10.2 DISCONTINUED SUBJECTS.

Discontinued subjects are those who voluntarily discontinue participation or who are lost to follow-up refer to section 5.8 for further details. Where possible, a full Exit Visit should be completed for all subjects who discontinue the study early. Where consent is withdrawn, the date and any reason given for discontinuation should be captured, at a minimum (see Section 5.8.2).

Finally, if appropriate, the Investigator will also advise the subject of subsequent therapy and/or procedures necessary for their medical condition.

Subjects who are withdrawn only from treatment will not automatically discontinue participation in the study, see Section 5.8.

10.3 SUBJECT PREGNANCY

Women of child-bearing potential are 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 subject will be withdrawn from study. Pregnancy is not 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.

10.4 STUDY METHODS AND MEASUREMENTS - CHRONIC WOUNDS AND DEHISCED SURGICAL WOUNDS ONLY.

10.4.1 SURGICAL DETAILS FOR DEHISCHED WOUNDS ONLY

Surgery details to be collected include the following questions:

- Date of surgical procedure (DD/MMM/YYYY).
- Collect surgery data [e.g. Type of surgery (type of surgery, method of closure and reference wound type and anatomical site).
- Collect surgery risk factors (elective/emergency surgery, laparoscopic (y/n), incision length, use of prophylactic antibiotics, type (single / double / triple agent) and when administered (prior to start of surgery/after surgery began), shaving of incision (yes / no / not needed), use of an incision drape (yes / no), clean/contaminated surgery (clean/clean-contaminated/contaminated/dirty), intraoperative warming (yes / no)).

10.4.2 WOUND ASSESSMENT.

Reference Wound Details Recorded at Initial Assessment

- Location of wound:
  - Upper leg;
  - lower leg;
  - knee;
  - ankle;
- Duration of wound (weeks/months/years)
- Previous Treatment (add options given in CRF)

- Has the reference wound been debrided? (Yes/No), if yes how?
- Has the reference wound been cleansed? (Yes/No. If yes, give detail of cleanser used).
- Reference wound measurement taken using the longest length, and width at right angles at midway point of length:
    - Length (cm);
    - Width (cm);
    - Depth (mm)
- Appearance of the reference wound using a Modified Bates-Jensen Wound Assessment Tool:
    - Necrotic Tissue Type: Pick the type of necrotic tissue that is predominant in the wound according to colour, consistency, and adherence using this guide:

White/grey non-viable tissue	=	May appear prior to wound opening; skin surface is white or grey.
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 centre or base of wound.
Firmly adherent, hard/black eschar	=	Firm, crusty tissue; strongly attached to wound base and edges (like a hard scab).

        - None visible
        - < 25% of wound bed covered
        - 25% to 50% of wound covered
        - 50% and < 75% of wound covered
        - 75% to 100% of wound covered

- 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 colour.
  - Skin intact or partial thickness wound
  - Bright, beefy red; 75% to 100% of wound filled &/or tissue overgrowth
  - Bright, beefy red; < 75% & > 25% of wound filled
  - Pink, &/or dull, dusky red &/or fills < 25% of wound
  - No granulation tissue present
- 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 the percent of wound involved and to measure the distance the epithelial tissue extends into the wound.
  - 100% wound covered, surface intact
  - 75% to < 100% wound covered &/or epithelial tissue extends to > 0.5 cm into wound bed
  - 50% to < 75% wound covered &/or epithelial tissue extends to < 0.5 cm into wound bed
  - 25% to < 50% wound covered
  - < 25% wound covered

- Level of Exudate
  - None;
  - Light;
  - Moderate;
  - Heavy
- Level of Pain since the last assessment (0-9; 0= no pain, 9 = maximum pain)
- Clinical judgement reference wound is clinically infected (Yes/No)

- Signs of clinical infection
    - None;
    - Wound static or deteriorating;
    - Increased exudate-secretion levels;
    - Increased pain;
    - Increased temperature around wound;
    - Discolouration of granulation tissue;
    - Friable granulation;
    - Tissue necrosis;
    - Local erythema;
    - Oedema;
    - Purulent drainage;
    - Odour;
    - Other

10.4.3 ASSESSMENT OF PERI-WOUND SKIN.

The surrounding skin will also be assessed by the above mentioned clinician. The clinician will assess whether the skin appears healthy or is fragile, inflamed, eczematous, dry/flaky, macerated or has erythema.

- Condition of peri-wound?
    - Normal
    - Erythematous
    - Oedematous
    - Eczematous
    - Excoriated
    - Macerated
    - Indurated
    -

10.4.4 CHRONIC WOUND SITE AND DRESSING PHOTOGRAPHS.

An image of the subject's will be captured prior to initial dressing application, at 7 days, 14 days, 21 days (or when dressing is removed) and at end of therapy at 28 days (or early exit visit) using a digital camera supplied by S&N. The images will be used as a pictorial record of the study reference wound.

A photo ruler labelled with the subject's number, study number and the date will be supplied by S&N and will be placed in the field of the photograph. The image should be framed such that the entire wound/dressing nearly fills the frame. Ensure that identifying information, such as the subject's face, are not visible in the photograph. After obtaining the image, ensure that the image is clear (in focus) and that there is sufficient light to clearly see the wound/dressing. Instructions for capturing images will be supplied with the cameras. Training on the use of the camera will be given during the site initiation visit.

An image of the dressing in place will be taken after application, and before removal, to check the device compliance.

If an AE or any other change to the subject's surgical site occurs during the study, further images of the wound will be captured to document the event if there is visible impact of the AE or other change. A photograph should also be taken where appropriate of all DevD reported.

All photographs should be uploaded to the relevant assessment on the CRF.

10.4.5 DRESSING APPLICATION ASSESSMENT.

Dressing Application information to be collected include the following questions.

To be completed for the reference wound (Day 0 – Treatment Discontinuation):

- Any products applied at dressing application (None/ SECURA No-Sting Barrier Film wipes / RENASYS Adhesive Gel Patch / topical antibiotics / other). Reduce bioburden, Lower risk of infection, Other.
    - Renasys gel patch used (Yes/No)
        - If used how long did the patch last for, and any problems upon removal.
        - Did the Renasys gel patch provide comfort to the subject's reference wound?

- PICO 14 **Pump UDI Number** 
- PICO 14 pump Lot Number and Catalogue number will also be collected.
- If Dressing used is separate to what is provided in the PICO14 kit please record UDI, Lot and Catalogue number of the dressing.
- Size of PICO 14 NPWT dressing kit size used (10 x 20 cm / 10 x 30 cm / 10 x 40 cm / 15 x 15 cm / 15 x 20 cm / 15 x 30 cm / 20 x 20 cm / 25 x 25 cm / Small Multisite / Large Multisite).
    - Was the dressing used on the chronic wound conformable (Yes/No)
      If No, please comment.
- Easy to create a vacuum on the PICO dressing (Yes / No).
- Easy to operate the pump on the PICO dressing (Yes / No).
- Dressing application on chronic wound:
    - Dressing easy to apply (Yes / No).
    - Satisfaction with the application of the PICO dressing (Yes / No).
    - Dressing comfortable (Yes / No).

<u>Question asked at all assessments from Treatment Discontinuation to Day 28 on wound</u>

- List the dressings that has been applied to the at this assessment (None / Steri-Strips / Foam dressing / Films/polymer dressing / Alginate/ Hydrofiber / Antimicrobial dressings (silver/iodine) / Hydrocolloid / Non-adherent dressing / Odour absorbent dressing / Absorbent pads / Bandages / Hydrogels / Gauze / Other).

10.4.6 DRESSING REMOVAL ASSESSMENT (AT DAY 14 AND DAY 28, ALSO APPLICABLE IF DRESSING HAS TO BE CHANGED BEFORE DAY 14/ DAY 28).

Dressing removal information to be collected include the following questions:

The dressing check indicator flashes routinely every 24 hours as a reminder to check the dressings. (Checked at day 1, 2, 3, 4, 5, 6 and 7 etc.) and (Checked by HCP/Patient).

To be completed for the chronic wound:

- Subject treatment setting (In-patient / Out-patient / Other).
- Dressing comfortable during wear (Yes / No. If no, please comment).
- Dressing acceptable to the patient (Yes / No. If no, please explain).
- Acceptable dressing exudate management (Yes / No. If no, please comment).
- Level of pain from the wound since the last assessment (0-10 scale).
- Reason for dressing change (Routine/ inadequate exudate management / pain-discomfort from the dressing / dressing damaged / dressing fell off / patient removed dressing / adverse event / surgical procedure / safety alarm / dressing components not in place / no vacuum /other).
- Is the dressing still covering the wound as applied? (Yes / No).
- How long has the dressing not covered the wound? (Day / Hour / Min) if applicable.
- Has the dressing been removed at any point since application? (Yes / No).
- How long was the dressing not in place? (Day / Hour / Min).
- Has there been any period that the vacuum was not applied during therapy apart from showering? (Yes / No. If yes, for how long).
- Level of Pain on removal of dressing (0 -10 scale).
- Was the dressing easy to remove? (Yes / No. If no, please comment).

10.4.7 TREATMENT DISCONTINUATION.

Treatment discontinuation information to be collected include the following questions,

- Date of treatment discontinuation.

- Reason for treatment discontinuation (End of treatment period (28 days) / Vacuum interrupted for > 48 hours / A change in treatment is clinically warranted / Subject withdrawn—Adverse Event / Other (specify). If Incision management complete.
- Overall subject assessment of PICO 14.
    - How was the pump carried around (Pump Clip / Pocket / Hand / Other? If other, please state). If the Pump Clip used, Was the clip a useful feature (Yes / No. If No, why).
    - Subject satisfaction with the following aspects of the NPWT system: Overall performance, Comfort during wear, Noise Level, Discreetness, Portability (Scale).
    - Interference with daily living – Showering, Sleeping, Socialising, Working (Yes, please comment/ No).
- Overall investigator assessment of PICO 14.
    - Overall is the Investigator satisfied with the performance of the PICO 14 system (pump and dressing) (Yes / No. If No please comment).
    - Following questions will be asked :"Are you satisfied with the PICO 14 systems ability to manage wound/ incision?", Are you satisfied with the PICO 14 systems ability regarding dressing retention?" and "Are you satisfied with the PICO 14 systems ability when compared to other NPWT devices?"

10.4.8 SUBJECT EXIT.

Subject exit information to be collected include the following questions,

- Date of Subject Exit.
- Reason for Subject Exit (end of therapy at day 28 / Subject Withdrawn – Non-compliance / Subject Withdrawn – Adverse Event / Subject Withdrawn – Subject's own request / Subject Withdrawn – Lost to follow-up / Investigator Decision / Other (Specify)).
- Complete exit questionnaire.

10.5 PICO 14 DEVICE RETURN.

All PICO 14 pumps will be returned to S&N for download of the in-built data chip. Once the pumps have been removed from the subject they are to be decontaminated using the following procedure:

- Label a zip-locked bag with subject ID number, initials and date labelled.
- At the Treatment Discontinuation Assessment the PICO dressing will be removed from the subject in order to inspect the surgical site as per the study protocol.
- The PICO dressing will be disconnected from the pump and the dressing disposed of as clinical waste.
- The surface of the pump should be wiped with a disinfectant wipe. Remove and retain the batteries. Clean the batteries and the inside of the battery compartment with a disinfectant wipe.
- Put the PICO pump and the batteries in the labelled bag.
- During the monitoring visits, the study monitor will count the devices and verify that they have been labelled correctly, collect devices and shipment will be arranged to Smith+Nephew Wound Management, Hull, UK.

In an identified handling area at Smith+Nephew Wound Management, Hull, UK, the devices shall be processed to have their internal memory contents downloaded, analysed and saved following an approved NPD (New Product Development) Work Instruction.

10.6 HEALTH ECONOMICS/QUALITY OF LIFE.

No Quality of Life Questionnaires will be collected for this study however, assessment of acceptability of the therapy will be made by specific targeted questions to the clinician and subject as described in section 11.4.5 above.

11. STATISTICAL DESIGN.

A Statistical Analysis Plan (SAP) will be written and finalized prior to database lock. The following is a brief description of the analyses to be described in this plan. The SAP will be more detailed and account for all analyses. All analyses will be conducted with statistical software SAS Version 9.4 or later.

11.1 GENERAL.

Smith+Nephew's Global Biostatistics group will conduct the statistical analysis for this study. The subject data will be described and summarised using the baseline demographic and medical variables which include but are not limited to age, gender, ethnicity, medical and medication history, diagnostic factors as well as study process variables (e.g. AE and withdrawal(s)). Summary statistics will be given according to the nature of the variable, continuous or categorical. For continuous variables, the number of observations, mean, standard deviation, median, minimum, and maximum will be presented, while for categorical variables the number of observations, frequency, and percentages will be reported. Summary statistics will be presented by wound type and by country, where appropriate.

Primary, secondary, and exploratory outcome variables and derived variables will also be summarised accordingly. Parametric statistical tests will be used if the data is normally distributed and corresponding non-parametric tests will be considered if the data is not. Where necessary, suitable regression techniques will be used to adjust for confounding since the study is non-randomised. Unless otherwise stated, the results will be reported at 5% significance level and where appropriate 95% confidence intervals will be given.

11.2 ANALYSIS POPULATIONS.

- Full analysis set population (FAS), including all subjects who were recruited into the study and have at least one post-baseline visit.
- Safety Population (SAF), including all subjects who have received the study device.
- Per-Protocol Population (PP), including all subjects in the full analysis set who have no significant protocol deviations and met the inclusion/exclusion criteria.

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

11.3 BASELINE DATA.

For chronic wounds and dehisced surgical wounds Day 0 (baseline) will be classified as the screening/ baseline visit. For closed surgical incisions Day 0 (baseline) will be classified as the operative day.

The subjects will be described and summarised using the baseline demographic and medical variables which include but are not limited to age, gender, ethnicity, medical and medication history, diagnostic factors. Summary statistics will be given according to the nature of the variable; continuous or categorical.

11.4 EFFICACY ANALYSIS.

The study will assess and evaluate the efficacy of PICO 14 by establishing equivalence in the mean operating negative pressure over a period of 14 days with a pressure of -80.2 mmHg. The clinical efficacy of PICO 14 will be concluded if statistically significant equivalence (within an equivalence margin of ±6mmHg) is achieved. Secondary and exploratory outcomes will be evaluated to consolidate the primary outcome analysis.

The study is non-comparative and non-randomised, the impact of confounding on the measures of efficacy may be expected and will be evaluated through fitting appropriate models and adjusting for potential factors.

11.5 ANALYSIS OF PRIMARY ENDPOINT.

- Delivery of -80mmHg negative pressure to the wound bed over the treatment period. This will be measured by download of the built-in data chip from the PICO 14 devices to collect NPWT delivery status.

The following hypotheses will be tested to establish equivalence of the PICO 14 integrated pump system compared to the literature value, with equivalence margin, $\delta_1>0$:

H_0: $|\mu - \mu_0| \geq \delta_1$

H_a: $|\mu - \mu_0| < \delta_1$

In the stated hypotheses, μ represents the assumed mean operating pressure taken from data extracted from a PICO sample device (-80.2 mmHg) and μ_0 represents the mean PICO 14 pump operating pressure.

The equivalence limit δ_1 = 6mmHg was chosen as a conservative non-clinically significant difference assuming that the difference is actually 0.

The average negative pressure across all subjects will be summarised as a continuous variable.

The difference between the average negative pressure from baseline to treatment discontinuation and the assumed mean negative pressure (-80.2mmHg) will be calculated for each subject separately. This difference for closed incisions, dehisced surgical wounds and chronic wounds combined will be assessed using a two one-sided t-test at the alpha level of 0.025. The mean difference will be presented along with the associated 95% confidence interval and if the 95% confidence interval lies fully within the equivalence boundaries (-6; 6) then the null hypothesis is rejected and clinical equivalence will be confirmed.

As an additional analysis the above will be repeated separately for each wound indication.

- No occurrence of exudate leaks observed during the dressing wearing period resulting or not, in an unplanned dressing change.

Occurrence of exudate leaks in the opinion of the clinician will be recorded in the CRF. For non-occurrence of exudate leaks, a binary variable indicating presence of/absence of will be defined. For the combined group (closed surgical incisions, dehisced surgical wounds and chronic wounds) the frequency together with percentage of reported/identified outcome will be reported with a 95% CI. This will also be summarised separately for each wound indication.

Logistic models will be fitted and important associated factors adjusted for if there is adequate data.

Composite Clinical Success (CCS) defined as a binary variable (1/0) (1 if both of the following are true and 0 if either one is false):

A. Nominal pressure is in the interval 80mmHg ± 6mmHg.

B. No exudate leakage.

The CCS will be reported as a count and percentage with a 95% CI for the combined group and separately for each wound indication.

11.6 ANALYSIS OF SECONDARY ENDPOINTS.

Closed Incision Only:

Clinical performance and safety of the PICO 14 NPWT system over a 14 day therapy and 30 day follow-up period to include:

- Scar quality measured by POSAS score at Day 14, and day 30.
- Incidence of Surgical Site Infection (SSI) and incidence of Surgical Site Complication (SSC) within 30 days of surgery [CDC criteria].
- Condition of peri-wound skin assessed through visual inspection at 7, 14 and 30 days.
- Level of pain on application, during wear and at dressing removal assessed by VAS scale over the 14 day treatment period.
- Patient satisfaction during wear assessed over the 14 day period. This includes leakage, feeling of moisture on the skin, odour control, level of protection, comfort and showerproof qualities.
- Ease of application and removal of the PICO 14 dressing.
- Dressing wear time.
- Dressing conformability
- Dressing change frequency and reason for dressing change.
- Clinician acceptability of PICO 14 system at discontinuation of therapy.
- Patient acceptability of PICO 14 system at discontinuation of therapy.

The POSAS consists of two parts: a Patient Scale and an Observer Scale. Each of the six items on both scales has a 10-point score. The lowest score is 1 and corresponds to the situation of normal skin (normal pigmentation, no itching etc.) and goes up to 10 indicating the worst imaginable. Total scores for both scales will be calculated separately by summing up the scores of each of the six items. An ‘Overall Opinion’ is scored separately of both patients and observers. Total scores and overall opinions will be summarised.

For incidence of SSC and incidence of SSI, binary variables indicating presence of/absence of will be defined. Total frequencies and number of subjects reporting each will be reported together with percentages.

Condition of the peri-wound (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated) will be summarised.

Level of pain on dressing application will be collected at Day 0 and for each dressing change assessment, level of pain during wear will be collected throughout the 14 day period, and level of pain on dressing removal will be collected at routine dressing changes and at the end of study visit. These will be measured using a VAS scale and will be summarised by wound type.

Patient satisfaction will be measured by overall performance of the dressing, comfort, noise level, discreteness, portability and interference with daily living – showering, sleeping, socializing and working. Summary statistics will be given according to the nature of the variable, continuous or categorical.

Ease of application, ease of establishing seal/negative pressure delivery, satisfaction of applying IP, knowing when to perform a dressing change and ease of removal will be reported by the clinician and frequencies will be summarised.

Dressing wear time (days) will be summarised as wear time per subject, by wound type and overall. Dressing change frequency will be summarised as the number of dressings per subject. Dressing conformability will be summarised as a categorical endpoint

Clinician and patient acceptability of PICO 14 system at discontinuation of therapy will be summarised through descriptive statistics and tabulated accordingly.

Chronic wounds and dehisced surgical wounds only:

Clinical performance and safety of the PICO 14 NPWT system over a 28 day therapy and no follow-up period to include:

- Incidence of clinical infection.
- Appearance of the wound in terms of tissue type and amount, exudate type and amount, skin condition surrounding the wound, peripheral tissue edema and induration.
- Condition of peri-wound skin assessed through visual inspection at 7, 14, 21 and 28 days.

- Percentage reduction in area, depth and volume from baseline to day 7, day 14, day 21 and day 28.
- Level of pain on application, during wear and at dressing removal assessed by VAS scale over the 28 day treatment period.
- Patient satisfaction during wear assessed over the 28 day period. This includes leakage, feeling of moisture on the skin, odour control, level of protection, comfort and showerproof qualities.
- Ease of application and removal of the PICO 14 dressing.
- Dressing wear time.
- Dressing conformability
- Dressing change frequency and reason for dressing change.
- Clinician acceptability of PICO 14 system at discontinuation of therapy.
- Patient acceptability of PICO 14 system at discontinuation of therapy.

Incidence of clinical infection will be summarised at all study visits and dressing changes by wound type and overall.

Appearance of the wound will be assessed by size, depth, edges, undermining, necrotic tissue type and amount, exudate type and amount, skin colour surrounding the wound, peripheral tissue edema and induration, granulation tissue and epithelialization. Numbers and percentages will be presented by wound type for baseline and Day 28. Condition of the peri-wound (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated) will be summarised.

The reference wound length, width and depth will be used to derive area and volume which will be summarised at each study visit. Percentage reduction in area and volume will be calculated and summarised using a Wilcoxon Signed Rank test from baseline to all post-baseline study visits.

Level of pain on dressing application will be collected at Day 0 and for each dressing change assessment, level of pain during wear will be collected throughout the 28 day period, and level of pain on dressing removal will be collected at routine dressing changes and at the end of study visit. These will be measured using a VAS scale and will be summarised by wound type.

Patient satisfaction will be measured by overall performance of the dressing, comfort, noise level, discreteness, portability and interference with daily living – showering, sleeping, socializing and working. Summary statistics will be given according to the nature of the variable, continuous or categorical.

Ease of application, ease of establishing seal/negative pressure delivery, satisfaction of applying IP, knowing when to perform a dressing change and ease of removal will be reported by the clinician and frequencies will be summarised.

Dressing wear time (days) will be summarised as wear time per subject, by wound type and overall. Dressing change frequency will be summarised as the number of dressings per subject. Dressing conformability will be summarised as a categorical endpoint

Clinician and patient acceptability of PICO 14 system at discontinuation of therapy will be summarised through descriptive statistics and tabulated accordingly.

11.7 ANALYSIS OF OTHER ENDPOINT(S).

There are no other endpoints planned for this study.

11.8 SAFETY ANALYSES.

- Adverse Events and Device Deficiencies.

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

Extent of Exposure

The duration of treatment will be summarised by wound type and overall.

Adverse Events

The number of subjects reporting: adverse events, serious adverse events, adverse device effects, serious adverse device effects and unanticipated serious adverse device effects will be summarized. In addition, for each adverse

event, the following will be summarized: severity, the relationship to the investigational device, outcome and duration of the resolved adverse events and the duration of the adverse events at trial discontinuation.

Device deficiencies

The number of device deficiencies and the number of patients reporting a device deficiency will be summarised. The number of device defficiencies leading to a serious adverse device effect will also be summarised and they will be listed along with any corrective actions taken (if any).

11.9 INTERIM ANALYSES.

There is no interim analysis planned for this study.

11.10 SAMPLE SIZE JUSTIFICATION.

Data extracted from a PICO sample device showed that the mean operating pressure was -80.2 mmHg (SD=14.8). It is assumed that all the PICO 14 pumps will have a similar mean operating pressure. The following hypotheses will be tested to establish the clinical equivalence in mean operating pressure of PICO 14 integrated pump systems over a period of 14 days compared to the sample PICO pump mean pressure (-80.2mmHg) with equivalence margin, $\delta_1>0$:

$$H_0: |\mu - \mu_0| \geq \delta_1$$

$$H_a: |\mu - \mu_0| < \delta_1$$

In the stated hypotheses, μ represents the assumed mean operating pressure of a PICO sample device (=-80.2mmHg, SD=14.8) and μ_0 represents the mean operating pressure of the study PICO 14 integrated pump systems. The equivalence δ_1 = 6mmHg was chosen as a conservative non-clinically significant difference for operating pressure assuming the difference is actually 0. The hypothesis will be tested by two one-sided t-test at the alpha level of 0.025. If the null hypothesis is rejected, clinical equivalence will be confirmed.

Based on data and assumptions used for sample size estimation (mean=-80.2mmHg, SD=14.8), a minimum of 55 subjects are required to achieve 80% power to detect equivalence at the significance level of α = 0.025 within

6mmHg using a two one-sided t-test (TOST) approach. Drawing from past experience, it is expected that approximately 20% of the subjects may be lost to follow up by the end of the study and therefore to account for this N=70 subjects will be recruited into this study. This will allow for a minimum of 10 subjects with each of the following indications to be recruited: Chronic open wounds (pressure ulcers, venous leg ulcers and diabetes-related foot ulcers), dehisced surgical wounds and closed surgical incisions (post-operative incisions following hip or knee arthroplasty).

The sample size was estimated using SAS V9.4.

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

12.1-1: Categories of Adverse Event

	NOT DEVICE-RELATED	DEVICE- OR PROCEDURE- RELATED	
Non-Serious	**Adverse Event (AE)**	**Adverse Device Effect (ADE)**	
Serious	**Serious Adverse Event (SAE)**	**Serious Adverse Device Effect (SADE) (See 12.1.3)**	
		Anticipated	**Unanticipated**
		Anticipated Serious Adverse Device Effect (ASADE)	**Unanticipated Serious Adverse Device Effect (USADE)**

12.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices.

AE is used both to refer to AE which do not meet the definitions of Adverse Device Effects or Serious Adverse Events 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 related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3: This includes "comparator" if the comparator is a medical device.

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 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, 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 RELATED 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, it led to any of the following:

a) death,

b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic diseases, 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) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

Note 1: 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 assessment.

Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

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.

Note 1: DD includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

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.

Coding for this study will be done per International Medical Device Regulators Forum (IMDRF) AE Terminology Annex E – Clinical signs, symptoms and conditions.

12.3 REPORTING PROCEDURES.

AE of any kind and DD will be recorded in the applicable CRF and source notes to include the date of occurrence, treatment and the details resolution. The Investigator will evaluate all AE for relationship to the device and procedure, seriousness, and severity (if applicable). 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)
- All other events – according to usual timescales

In addition to inputting SAE and SADE information within 24 hours of being aware of the event, the investigator should email Clinical.safety@Smith-nephew.com to alert the safety representative of the events existence and to clarify details if necessary.

For ADE and DD, date of occurrence, and 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 regulatory agency and IRB/IEC of adverse events as per the requirements listed below: -

Give timelines for applicable IRB/reg authority here.

If there is no clear timescale given by applicable IRB/reg authority then the following text should be used, otherwise delete:

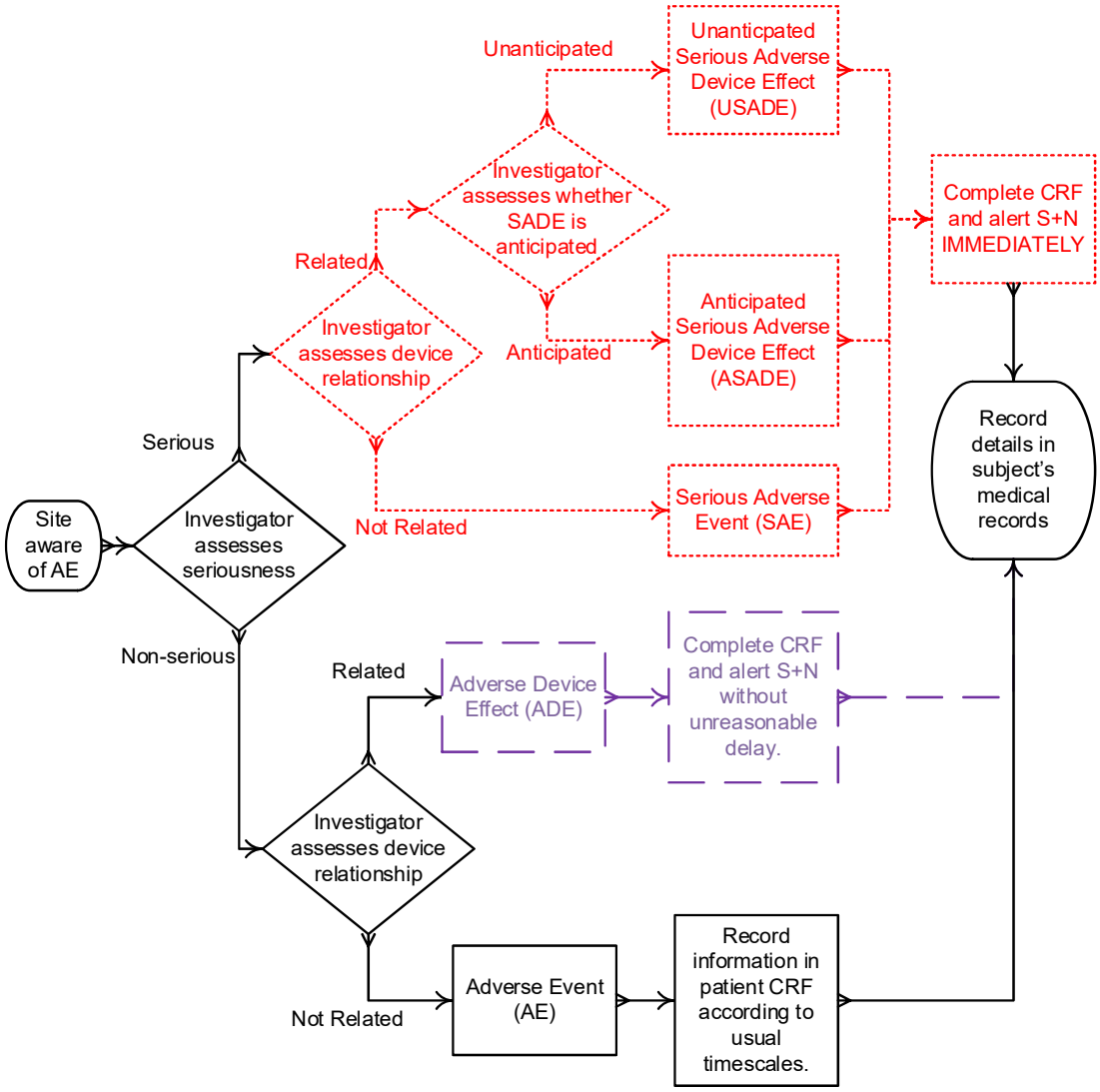
Unanticipated SADE's and DD's that could have led to SADE will be reported to IEC/IRB and regulatory authorities within 10 working days.

All other events will be reported on a periodic/annual basis.

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

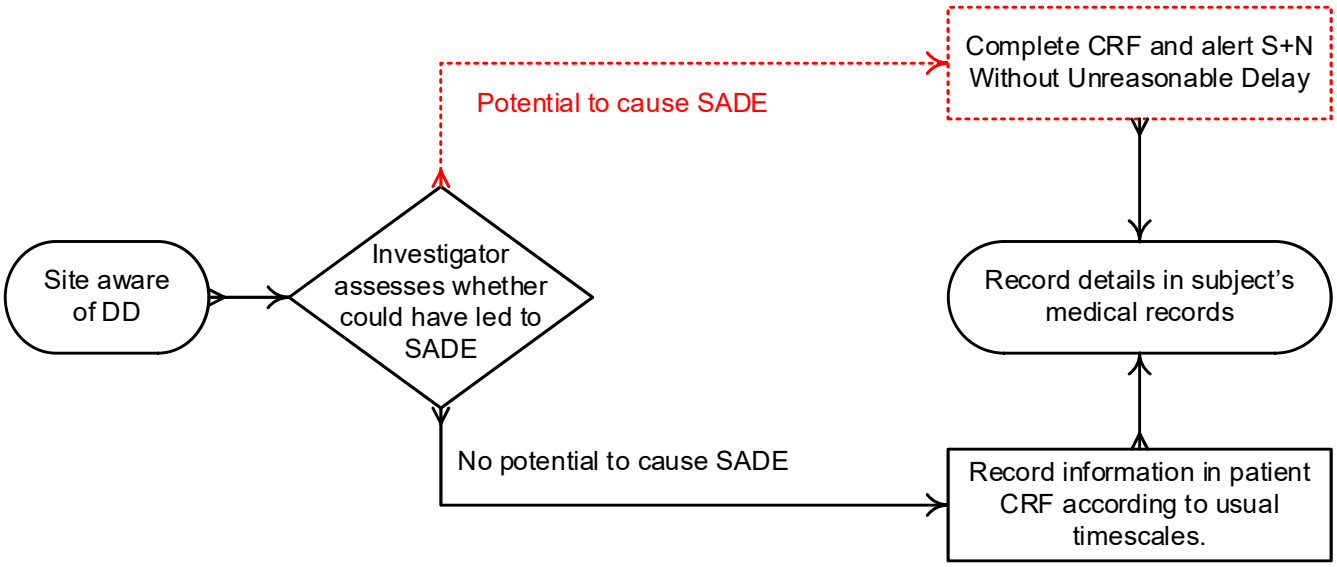
was hospitalized, a copy of the discharge summary may be requested by S+N and should be forwarded as soon as it becomes available. In certain cases, S+N also may request a letter from the Investigator that summarizes the events related to the case. Refer to the ISF Sponsor Contact Information Sheet to report SAE, unanticipated SADE, anticipated SADE, and DD.

Figure 12.3-12-1: Evaluation and Reporting of AE



13. EVALUATION AND REPORTING OF DD

Figure 13-1: EVALUATION AND REPORTING OF DD



13.1 UNBLINDING OF INVESTIGATIONAL PRODUCT.

This is not applicable as the study is not blinded.

13.2 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.

Any additional data must be documented and available to the Sponsor who will determine whether the data need to be documented in the CRF/Clinical Study Report.

13.2.1 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.

14. INVESTIGATOR OBLIGATIONS.

The Principal Investigator will comply with the commitments outlined in the in the Statement of Investigator, provided by the Sponsor/within the Clinical Trial Agreement>, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix 23.7 of this protocol.

In addition, the PI will ensure that the Financial Disclosure Statements will be completed by the PI and the Sub-Investigator upon entry into the study and as any changes that affect their financial disclosure status occur during the course of the study and up to one year after study completion.

15. 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.

15.1 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.

15.2 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 IRB/IEC approval.

15.3 INTERIM MONITORING VISIT

Regular interim monitoring visits will be performed by the Sponsor or qualified person designated by the Sponsor.

15.4 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.

15.5 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 IRB/IEC reporting requirements. When no subjects have been included, a remote close-out visit may be conducted.

16. PROTOCOL AMENDMENTS.

Amendments should be made only in necessary cases once the study has started. Protocol amendments must be approved by the protocol signatories prior to submission to the IRB/IEC. Protocol amendments need to be approved by the IRB/IEC and Regulatory Authority(ies), according to the applicable requirements prior to implementation at the site.

16.1 CONFIDENTIALITY OF THE STUDY.

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

16.2 STATEMENTS OF COMPLIANCE.

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

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

16.3 END OF STUDY.

The end of the study is defined as the last visit of the last subject undergoing treatment in the study. The expected duration of the study as defined from the first site initiated to the last subjects last visit is approximately 6 months.

Should any of the subjects suffer a complication during the course of the study, they will be analysed on an intention to treat basis and will be treated according to standard clinical care (that is considered to be the best care for the applicable coplication).

Early suspension or termination should only occur due to a safety issue since there is no interim analysis for this study and a full data set is required for BSI requirements and comparison of data to the pre-registration study.

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.

17. PUBLICATION POLICY

17.1 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.

17.2 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.

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19. APPENDICES

19.1 PROTOCOL AMENDMENT

Master Protocol Version 1.0 dated 7 Jan 2020 had to be amended to version 2.0 12 Mar 2021. The protocol amendment for this version is substantial and will go through UK ethics approval,

19.1.1 General Purpose

Reason for amendment:

- Inclusion and Exclusion criteria changes to allow for recent pandemic. Exclusion criteria change was also changed to reflect on the IFU that allows for participants to be included in study despite use of anti-coagulants.
- Change of informed consent processes to allow for Verbal consenting by sites if this is deemed necessary due to COVID 19 pandemic, also change in dehisced wound consenting to allow for emergency consenting.
- Allow for a new pathway to recruiting dehisced wounds.
- Change in number of sites to be included in the study.
- Changes were made to protocol to align with TMP-CD-05-01 REV D.1 as the template used is on REV A.

19.1.2 Rationale

Reason for amendment:

- REV D.1 is effective template for protocol with changes based on ISO14155.2020 and other regulatories, the template used for this study is on REV A, it is therefore important to align with the latest revision for compliance purposes.

- Pathway for recruitment has changed due to COVID pandemic and therefore it is important to accommodate for the changes and therefore change informed consent processes, change into dehisced wound recruitment, change the number of sites to increased recruitment rates post various lockdowns in UK.

19.1.3 Effect on Study Status

No effect on study, the changes will only allow for better recruitment rates in light of the COVID-19 pandemic. PIS and ICF changes made will be effective from date of Ethics approval and new versions will be used from that point.

19.1.4 Details

Section	Current Text DD/MMM/YYYY Version #	Revised Text DD/MMM/YYYY Version #
Smith+Nephew Logo	**07 JAN 2020 Version 1.0** **Logo used is Smith&Nephew.**	12 Sep 2021 VERSION 2.0 Changed logo throughout document Smith+Nephew
2 Synopsis Inclusion criteria	**07 JAN 2020 Version 1.0**	12 Sep 2021 VERSION 2.0 Additional description on Inclusion criterion for dehishced wounds, to allow for new pathway of recruitment.
2 Synopsis Exclusion criteria	**07 JAN 2020 Version 1.0** Patients with bleeding disorders, or concomitant use of anticoagulants.	12 Sep 2021 VERSION 2.0 Removed this exclusion criteria.
2 Synopsis	**07 JAN 2020 Version 1.0** Site numbers: up to seven.	12 Sep 2021 VERSION 2.0 Site numbers: up to ten.
7.3 Exclusion criteria	**07 JAN 2020 Version 1.0** Patients with bleeding disorders, or concomitant use of anticoagulants.	12 Sep 2021 VERSION 2.0 **Removed this exclusion criteria.**
7.5 Informed consent	**07 JAN 2020 Version 1.0** No verbal consenting permitted	12 Sep 2021 VERSION 2.0 Due to COVID-19 pandemic verbal consenting might be required by sites to achieve consent from participants who are unable to attend at the time of consent. Process for this will involve, site to provide PIS and full information on the study at least 24 hours prior to the Verbal call and consent. Verbal consent will be sought and the consenter will date and sign the ICF on the participant behalf, the participant will be screened thereafter and once in

		clinic they will be asked to sign and date the ICF personally.
7.5 Informed Consent		Added language to align with REV A to REV D.1 protocol template.
7.8.2 Withdrawal from study		Added language to align with REV A to REV D.1 protocol template.
8.3 Data Management		Added language to align with REV A to REV D.1 protocol template.
8.3.1 Data Review and Quality Assurance		Added language to align with REV A to REV D.1 protocol template.
8.3.2 Retention Period		Added language to align with REV A to REV D.1 protocol template.
9.1.7 Unscheduled Visit		Additional language added from REV A to REV D.1 protocol template. "All information obtained during an unscheduled visit should be recorded in the source documents and on the appropriate CRF."
9.1.10 Subject Pregnancy		Additional language added from REV A to REV D.1 protocol template." Pregnancy-related information will be collected until the end of the pregnancy."
12 Adverse Events and Device Deficiencies	REV A protocol template used for this section.	REV D.1 protocol template used for this section.
20.2 DATA sharing	REV A protocol template used for this section.	REV D.1 protocol template used for this section.

20. INSTRUCTIONS FOR USE

21. PRINCIPAL INVESTIGATOR OBLIGATIONS (ISO14155:2011)

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 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.

22. THE PATIENT AND OBSERVER SCAR ASSESSMENT SCALE (POSAS).

The POSAS consists of two parts: a Patient Scale and an Observer Scale. Both scales contain six items that are scored numerically and make up a 'Total Score' of the Patient and Observer Scale. The sum altogether will give the 'Total Score' of the POSAS. Besides the 10-step scale, category boxes are available to score nominal parameters (e.g. type of colour). Moreover, the patient and observer also score their 'Overall Opinion'.

The six items and Total Score of the Patient and Observer Scale POSASv2.0

Each item of both scales has a 10-point score, with 10 indicating the worst imaginable scar or sensation. The lowest score is '1', and corresponds to the situation of normal skin (normal pigmentation, no itching etc), and goes up to the worst imaginable. The Total Score of both scales can be simply calculated by summing up the scores of each of the six items. The Total Score will therefore range from 6 to 60. One may argue if the results of the separate items should be weighted to come to a more accurate Total Score. To date no convincing evidence is available that indicates that weighting improves the accuracy of the Total Score. Currently, the significance of weighting parameters is under investigation. Besides the six items the 'Overall Opinion' of the scar quality is scored separately of both patients and observers.

Categories (Observer Scale POSASv2.0)

Category boxes are provided to score the items not only quantitatively on a ten step scale but also qualitatively. In this way not only the severity but also the direction of the disorder (e.g., hypopigmentation or hyperpigmentation) is addressed. The categories are not included in calculating the Total Score of the POSAS. However, they are considered clinically relevant for complete documentation.

Overall Opinion (Patient and Observer Scale POSASv2.0)

Both the patient and the observer are asked to give their Overall Opinion on the appearance of the scar. Again, a 10-point scale is used in which 10 corresponds to the worst imaginable scar. The 'Overall Opinion' is not part of the Total Score of the Observer and Patient Scale of the POSAS.

Observer Scale POSASv2.0

In the POSASv2.0 observers rate vascularity, pigmentation, pliability, thickness, relief and surface area.

The directions for use of the different parameters of the Observer Scale POSASv2.0 are as follows (all parameters should be compared to normal skin at a comparable anatomical site whenever possible):

Vascularity: Presence of vessels in scar tissue assessed by the amount of redness, tested by the amount of blood return after blanching with a piece of Plexiglas Pigmentation: Brownish coloration of the scar by pigment (melanin); apply Plexiglas to the skin with moderate pressure to eliminate the effect of vascularity

Thickness: Average distance between the subcuticular-dermal border and the epidermal surface of the scar Relief: The extent to which surface irregularities are present (preferably compared with adjacent normal skin) Pliability: Suppleness of the scar tested by wrinkling the scar between the thumb and index finger Surface area: Surface area of the scar in relation to the original wound area

Furthermore the Overall Opinion is assessed as well as categories for each of the six items:

Vascularity*: pale | pink | red | purple | mix Pigmentation: hypo | hyper | mix Thickness*: thicker | thinner Relief*: more | less | mix Pliability*: supple | stiff | mix Surface area*: expansion | contraction | mix

* If more options are applicable please select the most suitable option.

Patient Scale POSASv2.0

The Patient Scale contains six questions applying to pain, itching, colour, pliability, thickness and relief. Because it was too difficult for patients to make the distinction between pigmentation and vascularity, both characteristics were captured in one item: colour. Each of the six items on both scales has a 10-point score, with 10 indicating the worst imaginable scar or sensation. The lowest score is '1', and corresponds to the situation of normal skin (normal pigmentation, no itching etc), and goes up to the worst imaginable.

The Patient Scale POSASv2.0 contains the following questions: 1. has the scar been painful the past few weeks? 2. Has the scar been itching the past few weeks? 3. Is the scar colour different from the colour of your normal skin at present? 4. Is the stiffness of the scar different from your normal skin at present? 5. Is the thickness of the scar different from your normal skin at present? 6. Is the scar more irregular than your normal skin at present?

These six items add up to the Total Score of the Patient Scale. Besides those six questions, the patient is asked to provide an Overall Opinion concerning scar quality.

Conditions for assessment

Ideally, scars should be evaluated clinically under the same conditions such as room temperature and humidity. At the time of measurement the skin and scar tissue of the patient should be adapted to this situation. Especially pigmentation may change because of seasonal variation.