Smith+Nephew

Clinical Protocol

[redacted] **Pre-Registration Clinical Study**

Sponsor Name and Address:	T. J. Smith & Nephew Medical Ltd., 101 Hessle Rd, Hull, HU3 2BN, UK
Investigational Product	[redacted] [redacted] NPWT system
Single Identification Number of Clinical Investigation	N/A
Protocol Author(s):	[redacted] Sr Clinical Study Manager [redacted] Sr Statistician II

1 SIGNATURES

1.1 Principal Investigator Signature Page

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

☐ I have read the attached protocol entitled "[redacted] Pre-Registration Clinical Study", version 9.0, dated 04/AUG/2021, and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in Section 22.10 of the protocol,

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

Name, Address, Professional Position	**Signature and Date / DocuSign Stamp**

1.2 Coordinating Investigator Approval

☒ I have read the attached protocol entitled "[redacted]Pre-Registration Clinical Study", version 9.0, dated 04/AUG/2021, and agree to abide by all provisions set forth therein.

Name, Address, Professional Position	**Signature and Date**
[redacted]	

1.3 Sponsor Approval

Name and Title	DocuSign Stamp
[redacted] Sr Director, Global Clinical Operations (Head of Global Clinical Operations)	[redacted]
[redacted] Sr Director, Clinical Strategies (Head of Global Clinical Strategy)	[redacted]
[redacted] Sr Director, Global Data Analytics (Head of Global Data Analytics)	[redacted]
[redacted] Medical Director (Medical Affairs Representative)	[redacted]
[redacted] Director, Regulatory Affairs (Regulatory Representative)	[redacted]

2 SYNOPSIS

Title of Study:	[redacted] Pre-Registration Study: Prospective, Multicentre Trial to assess performance and safety of [redacted]
Study Design:	• Prospective • Multi-centre • Non-randomised
Study Type:	Prospective Non-comparative
Study Product:	[redacted] [redacted] NPWT system
Comparison Group(s)*: (*if applicable)	NA
Study Purpose:	Pre-Market clinical trial to demonstrate performance and safety of the [redacted] system.
Primary Objective:	To assess the functional clinical performance of [redacted] NPWT system over 7 days therapy through the verification of delivery of negative pressure, wound exudate management and dressing wear time.
Secondary Objective(s):	To assess clinical performance and safety of the [redacted] NPWT system within 30 days of surgery through the: • Incidence of Surgical Site Infection (SSI) – Superficial, deep organ space [CDC criteria] • Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep etc.), seroma, necrosis, hematoma, suture abscess] • Condition of skin around the wound, and under the pump [redacted] • Any pain experienced by the subject in relation to the [redacted] system

Other Objective(s):	To assess clinician acceptability of [redacted] dressing at 7 days To assess subject acceptability of [redacted] dressing at 7 days To assess ease of application & removal of the [redacted] dressing To assess subject comfort during wear
Sample Size:	It was planned to recruit a total of 88 subjects to allow for 44 subjects to be recruited from each of the following specialties: orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions of which at least 50% would be colorectal cases). An interim analysis was made after 44 subjects were recruited (22 from each indication). Based on the root cause analysis of seal loss, the study will continue on Abdominal surgical indications only at this time, whilst further investigative work continues into understanding the cause of seal loss in the orthopaedic surgery group. The 2nd phase of the study (post-interim analysis) will be powered according to previous sample size. However, as no further subjects will be recruited for the orthopaedic surgery group, all 44 subjects recruited will be in the abdominal indication group. This will increase the total number of abdominal incisions to 66 (22 recruited following the protocol v7.0 and 44 following v8.0 of the protocol). This ensures that the primary endpoint is sufficiently powered for both the primary analysis of the abdominal data for all subjects as well as for a secondary analysis to be done on the data from those recruited according to protocol v8.0 only.
Number of Study Sites:	There were 6 sites involved in the first phase of recruitment (three sites for each of the specialties). Based on the interim analysis, the study will continue on abdominal surgical indications only, with 6 sites for the second phase of recruitment.

Targeted Global Regions:	UK
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 • In Orthopaedic surgery (*Phase 1 only*): subject is scheduled for an elective primary knee replacement arthroplasty and ASA score of 2-3 • In Abdominal surgery: subject is scheduled for an elective open or laparoscopic gastrointestinal and/or gynaecological surgery with incision ≥5 cm and has an ASA score of 2-3. • Immediately after the surgery, subject will have one suitable closed abdominal incision, (if there is more than one incision then the clinician should choose the one which in their opinion is most suited for [redacted] therapy) that fits under the absorbent dressing area of the appropriate [redacted] dressing sizes (dressing sizes equivalent to [redacted] dressings [redacted].
Exclusion Criteria:	• Contraindications (per the [redacted] IB) 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 with extremely fragile skin 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 similar clinical trial (wound care related) 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. • Subjects attending for an operation at the same surgery site (anatomical location) within the last 3 months. • Subjects undergoing a procedure as part of palliative care (to be confirmed during surgery). • Subjects where the [redacted] area of the device would be placed on a load-bearing anatomical location (i.e. areas vulnerable to pressure damage). • Subjects with incisions that are actively bleeding unless haemostasis has been achieved (to be confirmed during surgery). • Subjects with infected skin lesions or incisions at the time of surgery (any area of the body). • Subjects who have participated previously in this clinical trial • Subjects with a history of poor compliance with medical treatment. • Subjects with a BMI ≥ 40. • Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study. • Subjects where the dressing cannot be fully applied without coming into contact with, or covering, tubes, drains, wires or other ancillary devices which may affect the seal, and/ or which will require removal before the end of the seven day period
Study Duration:	Prior to the interim analysis, it was estimated that the study duration will be eighteen months from when the first study site is initiated until last enrolled subject reaches last study assessment. This period included an estimated 6-month period to prepare a mid-recruitment interim report, submit it and obtain feedback from MHRA. To reflect the much longer pause taken and time to secure approvals, the study duration is now expected to last 30 months.

Primary endpoint:	Functional clinical performance of [redacted] NPWT system over 7 days therapy to be assessed using a composite endpoint comprising the following components: • Negative pressure maintenance at nominal 80 mmHg as [redacted]. • Dressing wear time (7 days) [redacted] and CRF recorded data of any unplanned dressing change. • Exudate management assessed by no occurrence of exudate leaks as assessed through clinical data on any leakage of exudate through a dressing or around the borders observed during the dressing wearing period resulting or not, in an unplanned dressing change
Secondary endpoint(s):	Clinical performance and safety of the [redacted] NPWT system over a 30-day follow-up period to include: • Incidence of Surgical Site Infection (SSI) – Superficial, deep, organ [CDC criteria] within 30 days of surgery • Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep, partial/total), seroma, necrosis, hematoma, suture abscess] within 30 days of surgery • Condition of peri-wound skin and skin under the pump module assessed through visual inspection at 7, 14 and 30 days. • Wound and Skin VAS score assessment at 7, 14 and 30 days. • *Phase 1 only:* Range of motion assessment (ROM) for the knee at pre-operative visit, post-operative visit, 1, 7, 14 and 30 days. • Level of pain during wear of the [redacted] system, and at dressing removal assessed by VAS scale following 7-day therapy

Other exploratory endpoint(s):	• Clinician acceptability of [redacted] system at discontinuation of therapy • Subject acceptability of [redacted] system at discontinuation of therapy • Ease of application & removal • Subject comfort during wear
Safety Data	Safety, assessed through the incidence and severity of Adverse Events and Device Deficiencies.

STUDY SCHEDULE

Schedule of events	Pre-Operative Data (Up to 6 weeks pre-surgery)	Operative Data	Baseline Post-Operative Data (within 24 ± 3 hours)	Dressing Inspection 4 ± 1 day	End of Therapy Assessment 7 days	Day 14 FU (14 (± 3) days)	Exit Visit Day 30 FU (30 (± 3) days)	Unscheduled Visit or Early Exit
Informed Consent	x							
Inclusion/ Exclusion	x	x						
Demographics/Vital Signs/ Medical History/Hx of Substance Use	x							
Concomitant Medication Check	x	x	x	x	x	x	x	x
Subject Comfort Level and VAS Pain Score				x	x			
Acceptability of NPWT system to Subject					x			
Assessment of NPWT application by Clinician		x						
Acceptability of NPWT system to Clinician					x			
Instructions/Education For Subject &/Or Care Givers			x					
Operative Data Collection & Dressing application		x						
Range of Motion Assessment (for knee subjects - only in Phase 1)	x		x*		x**	x	x	

Schedule of events	Pre-Operative Data (Up to 6 weeks pre-surgery)	Operative Data	Baseline Post-Operative Data (within 24 ± 3 hours)	Dressing Inspection 4 ± 1 day	End of Therapy Assessment 7 days	Day 14 FU (14 (± 3) days)	Exit Visit Day 30 FU (30 (± 3) days)	Unscheduled Visit or Early Exit
Photographic & Incision Assessment		x			x	x	x	x
Treatment Data Collection & Dressing removal					x			
Incision complications assessment		x			x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x	x
Device Deficiency Assessment		x	x	x	x			
End of Study/Exit							x	x

*Post dressing application
**Pre and post-dressing removal

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3.4 List of Abbreviations and Definitions

Abbreviation	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
ASA	American Society of Anesthesiologists
ASADE	Anticipated Serious Adverse Device Effect
BMI	Body Mass Index
BSI	British Standards Institute
CCS	Composite Clinical Success
CDC	Centre for Disease Control & Prevention
CE	Conformité Européene
CER	Clinical Evaluation Report
CI	Confidence Interval
CoCr	Cobalt Chrome
CRF	Case Report Form(s)
CT	Computed Tomography
CTA	Clinical Trial Agreement
CRO	Contract Research Organization
CV	Curriculum Vitae
DD	Device Deficiency(ies)
EU	European Union
FAS	Full Analysis Set Population
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
HBO	Hyperbaric Oxygen Treatments

HIPAA	Health Information Portability Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
Interventional study	A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes.
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention to Treat population
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
NHS	National Health Service
Non-interventional study	A clinical study in which the investigational medical device of interest is used in accordance with the approved instructions for use. Assigning a subject/patient to a particular therapeutic arm is not decided in advance by a protocol but falls within current practice; use of the device is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are used, and epidemiological methods are used to analyze the collected data.
NPWT	Negative Pressure Wound Therapy

PI	Principal Investigator
PMA	Pre-Market Authorization
PP	Per-protocol Population
RCT	Randomized Controlled Trial
RFID	Radio Frequency Identification
ROM	Range of Motion
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
SSI	Surgical Site Infection
TGA	Therapeutic Goods Administration
TKA	Total Knee Arthroplasty
TÜV	Technischer Überwachungsverein/ Technical Inspection Association
Tx	Treatment
UK	United Kingdom
USADE	Unanticipated Serious Adverse Device Effect(s)
VAS	Visual Analogue Scale

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. Two surgical procedures that result in disruption to the skin tissue include closed abdominal

incisions and closed knee arthroplasty, each posing their own challenges in the healing process. Closed abdominal and closed knee arthroplasty incisions are alike in their characteristics with both involving primary closure of wounds following surgical procedures[1]. As a result, they encounter similar surgical site complications; however, the degree of risk of complications is likely to differ individually. Complications may consist of wound dehiscence, cellulitis, necrosis, superficial, deep and organ space surgical site infection, and delayed healing[2,3].

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%[3,4,5] and 9-12%[6,7,8] in closed abdominal and closed knee arthroplasty surgery 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[3,9,10]. In primary total knee arthroplasty the mean direct cost burden of 30 day readmissions has been shown as $13,008 and revision cases even higher at $29,893[11]. Although this figure encompasses all causes of readmissions it has been suggested that wound complications (including superficial infections, superficial dehiscence, and delayed healing) following total hip and knee arthroplasty may contribute heavily[12].

In addition to the financial burden, failure to heal can negatively impact patient's lives affecting physical, social, emotional and economic wellbeing[3,13]. 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[14,15]. In current literature use of NPWT has demonstrated a good success rates in closed abdominal incisions[18] and closed knee arthroplasty[17]. NPWT use on general surgery closed incisions has been reported to reduce surgical site complications including infection[18,19], dehiscence[20] and delayed healing[21]. This has also included some studies using single-use NPWT[22-24].

The PICO pump is a canister-free, disposable, single-use NPWT device which generates an effective negative pressure of 80 mm Hg25 and provides therapy for up to seven days. The PICO pump is connected to a conformable dressing which is designed to be easily applied and removed, while minimising skin trauma[26]. The device delivers negative pressure across the wound bed or closed incision[27] and surrounding area, and manages the fluid away from the wound or closed incision through a unique combination of absorbency and evaporation[25,27]. [redacted]

It is thought that NPWT may have numerous mechanisms of action when used to manage closed surgical incisions. 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[28]. Xia et al (2014)[29] demonstrated that in 20 subjects with infected wounds NPWT significantly increased blood flow in the wounds when compared to pre application levels.

Ultimately, the use of NPWT for closed abdominal incisions and closed knee arthroplasty has been linked to its clinical benefits, judged on the ability to minimise risk of surgical site complications. To enable NPWT to achieve this it must be amenable with patients and healthcare practitioner's requirements and so ensure compliance with the required negative pressure wound therapy protocols.

A summary of known and potential risks and benefits to humans of each Investigational Product (IP) can be found in the Investigator's Brochure (IB). For details of the full literature review, pre-clinical, clinical, safety data and a risk analysis refer to the IB.

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 closed surgically closed incision sites is a relatively new use of NPWT; despite this, it has still received reasonable attention within the literature. O'Leary et al[30] published in 2017 the results of a randomised controlled trial comparing the effect of PICO versus standard dressings on postoperative surgical site infection in closed laparotomy wounds. In 50 subjects (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[24] prospective study (2014), also using PICO, they assessed similar outcomes of surgical site events and compared results to a cohort using conventional dressings. Subjects enrolled in the study included those undergoing primary wound closure following breast or colorectal surgery. In the equally divided 50 subject 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 subjects treated with conventional dressings (7.1 days NPWT; 12 days control, p = 0.001). These findings have been further confirmed through a sub-group meta-analysis comparing PICO to standard care in abdominal surgery[23]. Selvaggi et al[25] published in 2014 the results of a prospective, open-label, controlled study comparing PICO with standard dressing in adults with Crohn's disease undergoing abdominal surgery. Main risk factors were the presence of Crohn's disease, smoking status, corticosteroids and ASA score 2-3. Twenty-five people were treated with PICO and 25 with the standard dressing. Subjects were followed for 12 months postoperatively. The primary endpoint was the 30-day rate of SSCs. Subjects treated with PICO had less SSC rates (OR 0.21, 95%CI 0.15-0.5, p=0.001) resulting in shorter hospital stay. At last follow-up, readmission rates were lower with PICO.

In revision hip and knee surgery Cooper and Bas (2016)[31] have previously compared the outcomes of closed incision NPWT and sterile antimicrobial dressing. In this 138 subject (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)[17] evaluated the use of PICO in subjects undergoing elective primary total hip and knee arthroplasties. Within this non-blinded randomised control trial 220 subjects were recruited and assigned to be treated with either incisional NPWT or conventional dressings. Their findings revealed that NPWT resulted in a 4 times lower number of surgical wound complications when compared to the conventional dressing group (2.0% NPWT; 8.4% control),however, in spite of the difference the results fell short close to statistical significance ($p = 0.06$). Results also showed 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[32], however this is not unanimously agreed upon for all NPWT systems[33].

Hudson et al (2015)[28] presented the results of a prospective, open label, non-comparative study. They assessed the functionality and performance of PICO in 20 subjects 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 PICO system to achieve near continuous negative pressure within therapy limits. This study has highlighted the ability and potential for newer systems to successfully deliver therapeutic levels of negative pressure.

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[25, 26, 34]. The size and simplicity gives patients confidence

that they can manage the system at home. This has implications in terms of cost savings for the health care system and allows the patient to return to their daily routine more quickly. [redacted]

4.3 Study Purpose

The study results will be used to generate data to support regulatory submission for CE marking. There is a need to generate clinical evidence for the [redacted] NPWT system to demonstrate safety and performance of the device. There is a significant amount of clinical evidence to show that PICO (1.5 &1.6) single use NPWT tethered pump systems may reduce oedema, increase healing rates and reduce chance of infection in closed surgical incisions. [redacted] This study will aim to assess the clinical performance and safety of the IP for the management of surgically closed incision sites. The clinical performance of the system will be assessed through a combination of, [redacted] and self-report (subject/clinician) data. This strategy was used successfully for the original PICO prototype and the initial information from clinical cases was published and used to support the capabilities of PICO technology[32,89]. When used on representative flat (abdominal laparotomy) and convex and mobile (knee arthroplasty, Phase 1 only) incisions, the [redacted]

4.4 Safety Consideration

The clinician should read the IB for [redacted] before use. The IB gives further details and additional information on [redacted] contraindications and precautions.

The following safety precautions, risks, warnings, contraindications and storage are relevant to this study:

Precautions

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted] has not been studied on paediatric subjects. Subject size and weight should be considered when prescribing this therapy.
- [redacted]
- Do not use [redacted] with oil-based products such as petrolatum as it may compromise the adhesive.

- For use on fragile skin, a skin protectant should be used where fixation strips are applied (e.g. NO-STING SKIN-PREP) as the fixation strips have a stronger, acrylic adhesive.
- [redacted] RENASYS Gel patches can be employed in awkward areas as a means to achieve a seal.
- The potential for electromagnetic interference in all environments cannot be eliminated. Use caution if [redacted] is near electronic equipment such as RFID (Radio Frequency Identification) readers, anti-theft equipment, or metal detectors.
- [redacted] is single use only. Do not reuse on more than one subject as this may lead to cross contamination, which may lead to infection.
- [redacted] should be applied immediately after removal from its sterile pouch. If it is necessary to carry this out in a home environment, then care should be made that the product does not come in contact with any children, pets or pests prior to application. If it is suspected that the product's sterility has been compromised, then do not apply. Obtain a new device and apply as indicated.
- [redacted]
- [redacted]

[redacted]

- High temperatures and humidity may affect wear time of [redacted]
- Do not cut absorbent component area as this may lead to loss of NPWT application.
- [redacted]
- When two [redacted] devices are applied, ensure borders do not overlap.

Risks

- There is a risk that patents will not receive therapy as intended if the dressing is not applied through use of the instructions in the IB. This risk will be mitigated by ensuring that: Clinicians shall be competent in the correct use of [redacted] prior to applying the dressing to the surgical sites of subjects.
- Clinicians will be directed to read and follow the IFU and IB.
- [redacted] will only be applied by a healthcare professional in line with the IB.
- Subjects will be trained in the use of the product and will be requested to refer to the IFU.
- Study personnel shall be directed to carefully follow the inclusion and exclusion criteria for participation in the [redacted] pre-registration study when assessing subject eligibility.

Warnings

- Excessive bleeding is a serious risk associated with the application of suction to wounds, which may result in death or serious injury. There should be

frequent monitoring for active bleeding. Additional caution should be given to those at a high risk of bleeding including:

- Subjects with weakened, friable or infected blood vessels.
- Wounds in close proximity to blood vessels or delicate fascia.
- Wounds with exposed sharp edges due to the risk of puncturing organs or blood vessels during therapy- Sharp edges should be covered or removed.
- Subjects without haemostasis established. With increased frequency of monitoring, [redacted] may be used with those on anticoagulants or platelet aggregation inhibitors.

- If pain, reddening, odour, sensitization or a sudden change in the volume or colour of wound fluid occurs during use the subject should contact their healthcare professional for assessment of an early dressing change.
- [redacted]
- Do not cover [redacted] in a manner that prevents regular inspection.
- [redacted] should only be applied and changed by a healthcare professional.
- Care should be taken that circumferential application or the use of negative pressure on ischemic limbs does not compromise circulation.
- [redacted]
- [redacted]
- [redacted]

Contraindications

The use of [redacted] is contraindicated in the presence of:

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

Storage

The [redacted] system must be stored between 5 and 25°C and relative humidity between 10-75%.

4.4.1 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.

4.4.2 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 subject 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.

4.4.3 OVERALL BENEFIT/RISK ANALYSIS

The anticipated medical benefits are considered to outweigh the overall or individual residual risks associated with [redacted] system within the proposed indication. The risks associated with PICO NPWT are addressed with reference to the warnings and precautions in the IB.

5 OBJECTIVE(S)

5.1 Primary Objective

To assess the functional clinical performance of [redacted] NPWT system over 7 days therapy through the verification of delivery of negative pressure, wound exudate management and dressing wear time.

5.2 Secondary Objective(s)

To assess clinical performance and safety of the [redacted] NPWT system within 30 days of surgery through the:

- Incidence of Surgical Site Infection (SSI) – Superficial, deep. [CDC criteria]
- Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep, partial/total), seroma, necrosis, hematoma, suture abscess]
- Condition of skin around the wound, and under the pump [redacted]
- *Phase 1 only:* Range of motion assessment (ROM) for the knee
- Any pain experienced by the subject in relation to the [redacted] system

5.3 Other Objective(s)

5.3.1 Exploratory

- To assess clinician acceptability of [redacted] dressing at 7 days
- To assess subject acceptability of [redacted] dressing at 7 days
- To assess ease of application & removal of the [redacted] dressing
- To assess subject comfort during wear

5.3.2 Safety

To assess Adverse Events and Device Deficiencies.

5.4 Claims

The study is being performed so that safety and clinical performance can be confirmed for the [redacted] product.

6 INVESTIGATIONAL PRODUCT

6.1 Identification

6.1.1 Investigational Product

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] –

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.1.2 Comparator Treatment

No comparator products will be used in this study.

6.1.3 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 Product Use

Sites will be requested to refer to the IB for full guidance on how the dressings and fixation strips should be applied for [redacted] The use of the PICO adhesive

strips are mandatory for the IP per the application instructions in the IFU and IB. All sites will be trained in and experienced in the use of [redacted] 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 [redacted] if required, to minimise learning effects prior to the live phase of the study. Previous experience with PICO should include use on incision sites and not limited to open or chronic wounds.

6.2.1 Investigational product – [redacted]

The [redacted] single-use NPWT system should only be applied by a healthcare professional using a clean technique throughout application and removal. Refer to Appendix 21.2 – [redacted] User Manual for full details and diagrams of the Instructions for Use.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.2 Ancillary product

Do not use SECURA No-Sting Barrier Film wipes or RENASYS Adhesive Gel Patches on any subjects with known allergy to the ingredients. Avoid contact with the eyes. RENASYS Adhesive Gel Patches should only be used on intact skin. There are no other special considerations for use of these products.

6.3 Packaging and Labelling

Packaging and labelling will be prepared to meet regulatory requirements.

Package integrity and labelling should be verified prior to use of the product and confirmed in the CRF.

6.3.1 Labelling of Investigational Product

Labels on the Primary Packaging contain the following information

- Study number

- Lot number
- Expiry Date
- Site number and address
- Place for the Subject number and Initials
- Place for Visit Date if applicable
- Exclusively for Clinical Investigation
- T. J. Smith & Nephew Medical Ltd., Hull, UK

The labels on the IP secondary packaging contain the following information

- Study number
- Lot/batch number
- Expiry date
- Site number and contact details
- Place for the Subject number and Initials
- Place for Visit Date
- Storage conditions
- Exclusively for Clinical Investigation
- T. J. Smith & Nephew Medical Ltd, Hull, UK
- See IFU/IB
- Return all unused product at end of study

6.3.2 Comparator Product

This section is not applicable.

6.3.3 Ancillary Product

This section is not applicable as all ancillary product supplied is commercially available and used within its approved indications.

6.4 Product Accountability Procedures

The investigational site will maintain an inventory of the IP. Overall accountability is by the Investigator or designated individual maintaining an inventory, which will include details of receipt, use, waste, returns, and collection etc. by the Sponsor of the IP. Accountability records must document which products (batch, expiry, quantity) were used by which subjects. The Sponsor will provide log(s) to facilitate IP inventory control. All IP 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 appropriate reconciliation of all IP. As part of monitoring, the Study Monitor will check that the site personnel are following the proper procedures for accountability and completing all necessary documentation.

During transit to the site and storage at the site, temperature loggers will be used to ensure that the IP does not fluctuate outside the recommended temperature for maintenance of the product components.

7 SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 Subject Population

The original plan was to recruit a total of 88 subjects to allow for 44 subjects to be recruited from each of the following specialties: orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions of which at least 50% would be colorectal cases). There were 6 sites involved in the first phase of recruitment (three sites for each of the specialties).

An interim analysis was made after 44 subjects were recruited (22 from each indication). Based on the root cause analysis of seal loss, Phase 2 of the study will continue on Abdominal surgical indications only at this time, whilst further investigative work continues into understanding the cause of seal loss in the orthopaedic surgery group.
The 2nd phase of the study (post-interim analysis) will be powered according to previous sample size. However, as no further subjects will be recruited for the orthopaedic surgery group, all 44 subjects recruited will be in the abdominal indication group.

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 (reference section 7.5).

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.	Subject is suitable to participate in the study in the opinion of the Investigator
6.	*(Phase 1 only)*: In Orthopaedic surgery: subject is scheduled for an elective prim knee replacement arthroplasty and ASA* score of 2-3.
7.	In Abdominal surgery: subject is scheduled for an elective open or laparoscopic gastrointestinal and/or gynaecological surgery with incision ≥5 cm and has an ASA score of 2-3.
8.	Immediately after the surgery, subject will have one suitable closed abdominal or knee surgery incision(Phase 1 only), (if there is more than one incision, then the clinicians should choose the one which in their opinion is most suited to PICO therapy) that fits under the absorbent dressing area of the appropriate [redacted] dressing sizes [redacted]

*American Society of Anesthesiologists (ASA) Physical Status Classification System. See Appendix 22.11

7.3 Exclusion Criteria

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

1.	Contraindications (per the [redacted] IB) 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 similar clinical trial (wound care related) 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.	Subjects attending for an operation at the same surgery site (anatomical location) within the last 3 months.
6.	Subjects undergoing a procedure as part of palliative care (to be confirmed during surgery).
7.	Subjects where the [redacted] area of the device would be placed on a load-bearing anatomical location (i.e. areas vulnerable to pressure damage).
8.	Subjects with incisions that are actively bleeding unless haemostasis has been achieved (to be confirmed during surgery).
9.	Subjects with infected skin lesions or incisions at the time of surgery (any area of the body).

10.	Subjects who have participated previously in this clinical trial.
11.	Subjects with a history of poor compliance with medical treatment.
12.	Subjects with a BMI ≥ 40.
13.	Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.
14.	Subjects where the dressing cannot be fully applied without coming into contact with, or covering, tubes, drains, wires or other ancillary devices which may affect the seal, and/ or which will require removal before the end of the seven day period

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 Enrolment Log. All screening activities which occur prior to consent shall be referred to as pre-screening.

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 9.1.2 and 9.1.3). 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 ample time (at least 24 hours) to consider participation following the explanation of the study/reading of the patient information sheet. 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 Enrolment

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 7 day, 14 day, or 30 day 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 prior to declaring a subject to be lost to follow-up: the subject has been contacted according to the site's policies, but no fewer than 2 documented phone contacts and 1 certified letter without response. Copies of all attempts to reach the subjects per regular mail or email and/or the attempts to contact the subject via other means should be documented and that documentation should be kept with the subject's source documents.

7.8 Withdrawal

7.8.1 Withdrawal from Treatment

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 or the investigator, 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 7-day therapy).
    - 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 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
- 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 withdrawn prior to the application of the study dressing will be replaced.

Subjects who are treated for bilateral knee surgery, 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 in 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

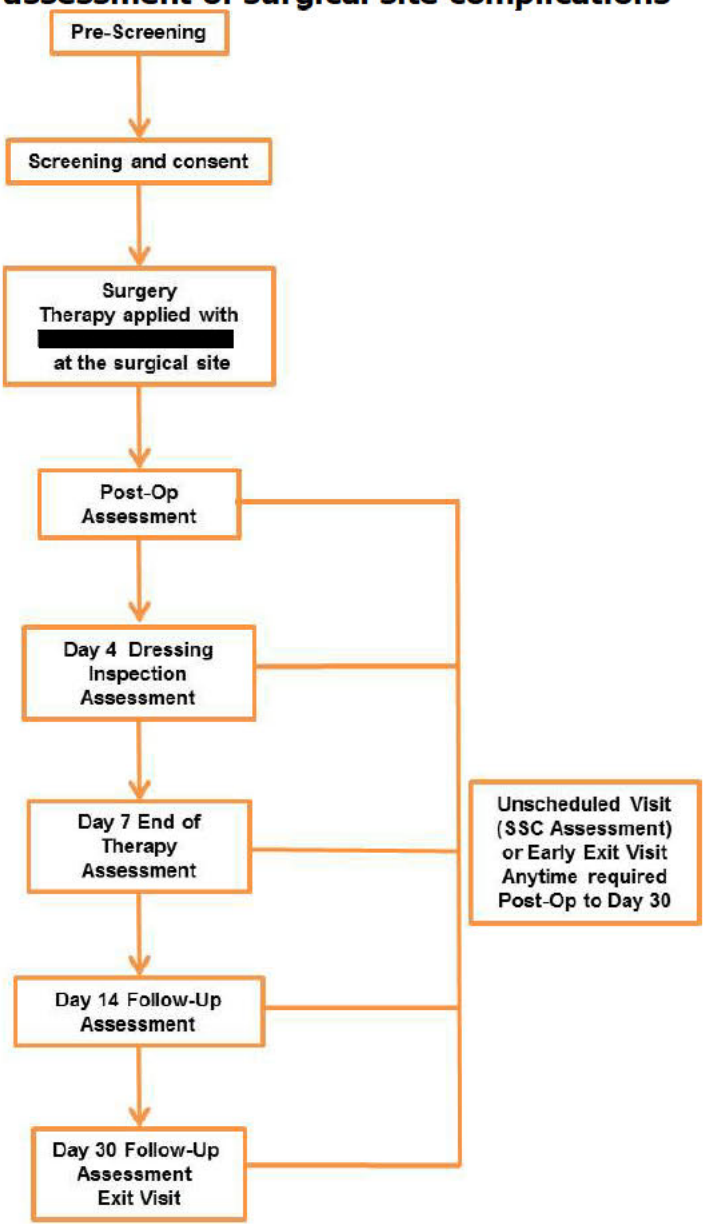
8.1 Study Design

This study is a prospective, multi-centre, non-randomised, non-blinded, single arm follow-up study to assess clinical performance and safety of [redacted] It is anticipated that up to 6 sites will participate within the UK.

The treatment phase will be 7 days post-surgery with a study follow-up period up to 30 days for assessment of complications. Seven days of therapy has been chosen as the length of time to assess device performance 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. The 30 day time period to assess safety and complications is given since previous literature suggests that most complications may occur during the first 30 days following surgery.

Figure 2 Study Flowchart - Schedule of [redacted] follow-up for assessment of surgical site complications



8.2 Allocation and Blinding

This study is non-randomised.

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.

8.3.1 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.

8.3.2 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.

8.4 Study Endpoints

8.4.1 Primary Endpoint

Functional clinical performance of [redacted] NPWT system over 7 days therapy to be assessed using a composite endpoint including the following components:

- Negative Pressure maintenance at nominal 80 mmHg [redacted].
- Dressing wear time (7 days) as assessed through a combination of [redacted] and CRF recorded data of any unplanned dressing change.
- Exudate management assessed by no occurrence of exudate leaks as assessed through clinical data on any leakage of exudate through a dressing or around

the borders observed during the dressing wearing period resulting or not, in an unplanned dressing change.

8.4.2 Secondary Endpoints

Clinical performance and safety of the [redacted] NPWT system over a 30 day follow-up period to include:

- Incidence of Surgical Site Infection (SSI) – Superficial, deep, organ [CDC criteria] within 30 days of surgery
- Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep, partial/total), seroma, necrosis, hematoma, suture abscess] within 30 days of surgery
- Condition of peri-wound skin and skin under the pump [redacted] assessed through visual inspection at 7, 14 and 30 days.
- Wound and Skin VAS score assessment at 7, 14 and 30 days
- *Phase 1 only:* Comparison of Wound and Skin VAS scores at days 7, 14 and 30 as assessed by the treating clinicians versus scores provided by the independent assessor.
- *Phase 1 only:*Range of motion assessment (for knee subjects only) at pre-operative, post-operative day 1, 7, 14 and 30 days
- Level of pain during wear of the [redacted] system, and at dressing removal assessed by VAS scale following 7-day therapy

8.4.3 Exploratory Endpoints

- Clinician acceptability of [redacted] system at discontinuation of therapy
- Subject acceptability of [redacted] system at discontinuation of therapy
- Ease of application & removal
- Subject comfort during wear.
- A descriptive analysis for clinician's and subject's experience of the device and perception of the device in general will be included in the analysis.

8.4.4 Safety Endpoints

Safety, assessed through the incidence and severity of Adverse Events and Device Deficiencies

8.5 Methods Used to Minimize Bias and Maximize Validity

8.5.1 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 [redacted] 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.clintrials.gov and any other applicable trial registries.

8.5.2 Minimisation of bias due to low study numbers

The statistical techniques for the study have attempted to account for bias brought about by low subject numbers. Subject attrition has been accounted for within the sample size calculation. This sample size was based on a previous PICO study data using similar data loggers.

8.5.3 Attempt to retain ecological validity

Phase 1 of the study included a single indication in two different surgical specialties and a range of contoured areas of the body where it may be difficult to obtain an effective negative pressure seal and where there may be a range of motion throughout therapy (i.e. knee). The inclusion/exclusion criteria are also not too restrictive with regard to subject demographic. This should mean that the results will be representative of a real clinical setting in hospital or at home, and for the proposed indication in the two specialties.

8.5.4 Attempt to reduce ascertainment bias in data collection

Subject and clinician will also be requested to verify any answer they give with some rationale for their answer where possible.

9 STUDY PROCEDURES

9.1 Visits and Examinations

9.1.1 Summary

Figure 3 Study Procedures by Visit

Schedule of events	Pre-Operative Data (Up to 6 weeks pre-surgery)	Operative Data	Baseline Post-Operative Data (within 24 ± 3 hours)	Dressing Inspection 4 ± 1 day	End of Therapy Assessment 7 days	Day 14 FU (14 (± 3) days)	Exit Visit Day 30 FU (30 (± 3) days)	Unscheduled Visit or Early Exit
Informed Consent	x							
Inclusion/ Exclusion	x	x						
Demographics/ Vital Signs/ Medical History/History of Substance Use	x							
Concomitant Medication Check	x	x	x	x	x	x	x	x
Subject Comfort Level and VAS Pain Score				x	x			
Acceptability of NPWT system to Subject					x			
Assessment of NPWT application by Clinician		x						
Acceptability of NPWT system to Clinician					x			

Schedule of events	Pre-Operative Data (Up to 6 weeks pre-surgery)	Operative Data	Baseline Post-Operative Data (within 24 ± 3 hours)	Dressing Inspection 4 ± 1 day	End of Therapy Assessment 7 days	Day 14 FU (14 (± 3) days)	Exit Visit Day 30 FU (30 (± 3) days)	Unscheduled Visit or Early Exit
Instructions/ Education For Subject &/Or Care Givers			x					
Operative Data Collection & Dressing application		x						
Range of Motion Assessment (for knee subjects in phase 1 only)	x		x*		x**	x	x	
Photographic & Incision Assessment		x			x	x	x	x
Treatment Data Collection & Dressing removal					x			
Incision complications assessment		x			x	x	x	x
Adverse Event Assessment		x	x	x	x	x	x	x
Device Deficiency Assessment		x	x	x	x			
End of Study/Exit							x	x

* post dressing application

** Pre and post dressing removal

9.1.2 Screening/Preoperative Visit (may be up to 6 weeks prior to operative visit)

NOTE: Any subject who signs an informed consent but fails to meet the required entry criteria is considered to be a Screen Failure. Information must be captured in the appropriate CRFs up to the point of screen failure with the reason for screen failure specified (section 7.4).

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 (for current or chronic conditions as per the eCRF categories), including information on all concomitant medications/therapies.
3.	Screen the subject for protocol inclusion/exclusion criteria.
4.	Obtain range of motion measurements (for knee subjects only in Phase 1)
5.	Subjects will be instructed to return to the treatment facility for the Operation Visit (within 6 weeks of consent).

9.1.3 Baseline Operative Visit (Within 6 weeks of screening)

NOTE: Any subject who has signed an informed consent but at this visit no longer meets the required eligibility criteria prior to the study dressing application is considered to be a Screen Failure. Information must be captured in the appropriate CRFs up to the point of screen failure with the reason for screen failure specified (section 7.4).

1.	Query subject regarding any changes in general health and the use of concomitant medications (if screening and surgery are not on the same date).
2.	Commence operation and collect surgery data [e.g. Type of surgery (closed surgical incision, (type of abdominal surgery, type of knee surgery, incision length, anatomical location and method of closure),
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), surgical bioburden level(clean/clean-contaminated/ contaminated/dirty), intraoperative warming (yes/no))
4.	Confirm eligibility following surgery details. NOTE: Subjects that no longer meet the eligibility criteria following surgery will be deemed a screen failure; operative information must be captured in the appropriate CRF with the reason for screen failure specified. These subjects will be replaced.
5.	Photograph incision using the camera ([redacted] provided by the Sponsor.
6.	Assess the incision characteristics for likelihood of SSC (oedema, seroma, haematoma, skin necrosis.
7.	Assess the surrounding skin including the area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated).
8.	Dispense study product. Record pump lot number, size of dressing used [redacted] and any ancillary products applied (SECURA No-Sting Skin prep, RENASYS Adhesive Gel Patch). Record also ancillaries in the vicinity (e.g. drains, stomas, lines, dressings).
9.	Assess ease of application, ease of establishing seal/negative pressure delivery, satisfaction of applying IP.
10.	Take photograph of dressing in place. Take a photograph of the carton label to aid accountability checks (the label will contain the batch number).
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.
12.	If there were failed attempts at applying the study product. Please record the device details and disposition of the device.

9.1.4 Baseline Post-Operative Visit (within 24[±3 hours] if subject is well enough and coherent

1.	Record the use of concomitant medications.
2.	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.

3.	Obtain range of motion measurements (for knee subjects only in Phase 1)
4.	Instruct the subject on proper post treatment/postoperative care/procedures, including any contraindicated treatments/medication(s) and refer subject to the IFU.
5.	Instruct the subject on follow-up procedures, including returning to the treatment facility for the Day 4 Follow-Up (FU) Visit in 4 days ±1 day post-surgery.

9.1.5 Day 4(± 1 day) 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 4 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 (VAS pain scale).
7.	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.
8.	Instruct the subject on follow-up procedures, including returning to the treatment facility for the End of Therapy Assessment Visit at 7 days post-surgery.

9.1.6 End of Therapy Assessment (7 days unless therapy is to be stopped sooner due to clinical need)

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 7 days, record reason (e.g. [redacted] NPWT system removed, treatment interrupted for 24 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 the use of concomitant medications.
4.	Record reason if dressing is no longer in place (e.g. pain/discomfort from the dressing, subject removed, subject'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.	Obtain range of motion measurements (for knee subjects only in Phase 1)
8.	Assess subject satisfaction (overall performance of dressing, comfort, noise level, discreteness, portability, interference with daily living – showering, sleeping, socialising, working).
9.	Remove NPWT system as per procedure (section 9.2.4) for [redacted]. Record the unique device identifier [redacted]).
10.	Assess ease of removal.
11.	Record pain score (VAS) and subject comfort since last assessment and pain score on dressing removal.
12.	A suitably qualified individual (as described in section 9.2.1) to complete CDC incision assessment and incision closure.
13.	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 additional procedures to be collected (per section 9.1.9).
14.	Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)
15.	Assess the skin area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)
16	Obtain range of motion measurements (for knee subjects only in Phase 1)
17.	Photograph the incision using the camera ([redacted] supplied by the Sponsor. The wound photographs and the resulting wound measures will be stored in a database.
18.	Record 100mm VAS score for wound and skin assessment

19.	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.
20.	Follow procedure for removal, appropriate labelling and storage of [redacted] in IP.
21.	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).
22.	Instruct the subject on follow-up procedures, including returning to the treatment facility for the Day 14 FU Visit 3 at 14 (±3) days post-surgery.

9.1.7 Day 14 Follow-Up (14[± 3] days

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	A suitably qualified individual (as described in section 9.2.1) to complete CDC incision assessment and incision closure.
3.	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 9.1.9).
4.	Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated).
5.	Assess the skin area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)
6	Obtain range of motion measurements (for knee subjects only in Phase 1)
7.	Photograph the incision using the camera ([redacted] supplied by the Sponsor. The wound photographs and the resulting wound measures will be stored in a database.
8.	Record 100mm VAS score for wound and skin assessment
9.	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.
10.	Instruct the subject on follow-up procedures, including returning to the treatment facility for the Exit Visit at 30 (±3) day post-surgery.

9.1.8 Exit Visit (30 (± 3) days)

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	A suitably qualified individual (as described in section 9.2.1) to complete CDC incision assessment and incision closure.
3.	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 9.1.9).
4.	Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)
5.	Assess the skin area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)
6.	Obtain range of motion measurements (for knee subjects only in Phase 1)
7.	Photograph the incision using the camera ([redacted] supplied by the Sponsor. The wound photographs and the resulting wound measures will be stored in a database.
8.	Record 100mm VAS score for wound and skin assessment
9.	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.
10.	Complete Exit Visit CRF

9.1.9 Unscheduled Visits-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 operative, post-operative, end of therapy assessment, or 30 day exit, visits.

1.	Record the date that the complication occurred.
2.	Record the complication type. Please provide as much detail as possible.
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 (e.g. a different NPWT system, simple foam dressing, antimicrobial dressing, other). Photograph the incision using the camera ([redacted] supplied by the Sponsor. The wound photographs and the resulting wound measures will be stored in a database. Record 100mm VAS score for wound and skin assessment.
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.

9.1.10 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.

Concomitant Medications

Excluded Concomitant Medications

The following concomitant medications are not permitted from the time of enrolment 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 IB (other than the SECURA skin barrier wipes and RENASYS Adhesive Gel Patches provided as ancillary for the study).

Recording Concomitant Medications in CRF

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

Concomitant Therapies

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, wound contact layers) should be used under the IP during therapy.
- 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.

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.

9.1.11 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation or who are lost to follow-up refer to section 7.8 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 7.8.2).

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 7.8.

9.1.12 Subject Pregnancy

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

9.2 Study Methods and Measurements

9.2.1 Incision Closure, SSC and CDC-SSI Incision Assessment

Incision closure is defined as 100% re-epithelisation without drainage or dressing requirements. Primary or first intention healing occurs when tissue is cleanly incised and re-approximated and healing occurs without complications. The incisional defect re-epithelises rapidly and matrix deposition seals the defect. Incisional wounds are usually completely re-epithelised 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 healing and potential complications will be completed by a suitably qualified individual at each of the specified time points. The assessment will be performed using the CDC definitions of surgical site infection. SSI are infections that occur within 30

days of surgery or within a year if an implant is present. In addition, one of the following criteria must be met:

(1) Purulent drainage from an incision (incisional infection) or from a drain below the fascia (deep infection);

(2) A surgeon or attending physician diagnosing an SSI;

(3) An infective organism being isolated from a culture of fluid or tissue obtained from the surgical wound (for incisional infections);

(4) Spontaneous dehiscence or a surgeon deliberately re-opening the wound in the presence of fever or local pain, unless subsequent cultures were negative, or an abscess being detected during direct examinations (for deep infections). The grading of SSI is based on symptoms.

In case of SSI, there may be also discharge (serous exudate, seropurulent, haemopurulent, pus), delayed healing, erythema, unexpected pain, tenderness, abnormal smell or wound breakdown.

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). Wound dehiscence will also be classified as partial or total.

The wound size measurements will be performed directly from the wound photographs taken from the wound per each visit. The camera ([redacted] will measure the lengths, the depth and the width of the wound automatically, if appropriate. The wound photographs and the resulting wound measures will be stored in a database.

Assessment of the wound will also include the use of a validated 100 mm Visual Analogue Scale (VAS) as described by Keeney et al [35], where a very low score is associated to a wound with a major gapping, dehiscence, severe inflammation and/or infection; and a very high score correspond to a completely healed wound with no evidence for inflammation. VAS

assessment for wound evolution will be performed by a qualified clinician at each research centre.

Representative images for guidance on the use of the validated 100 mm VAS scale are presented here below.

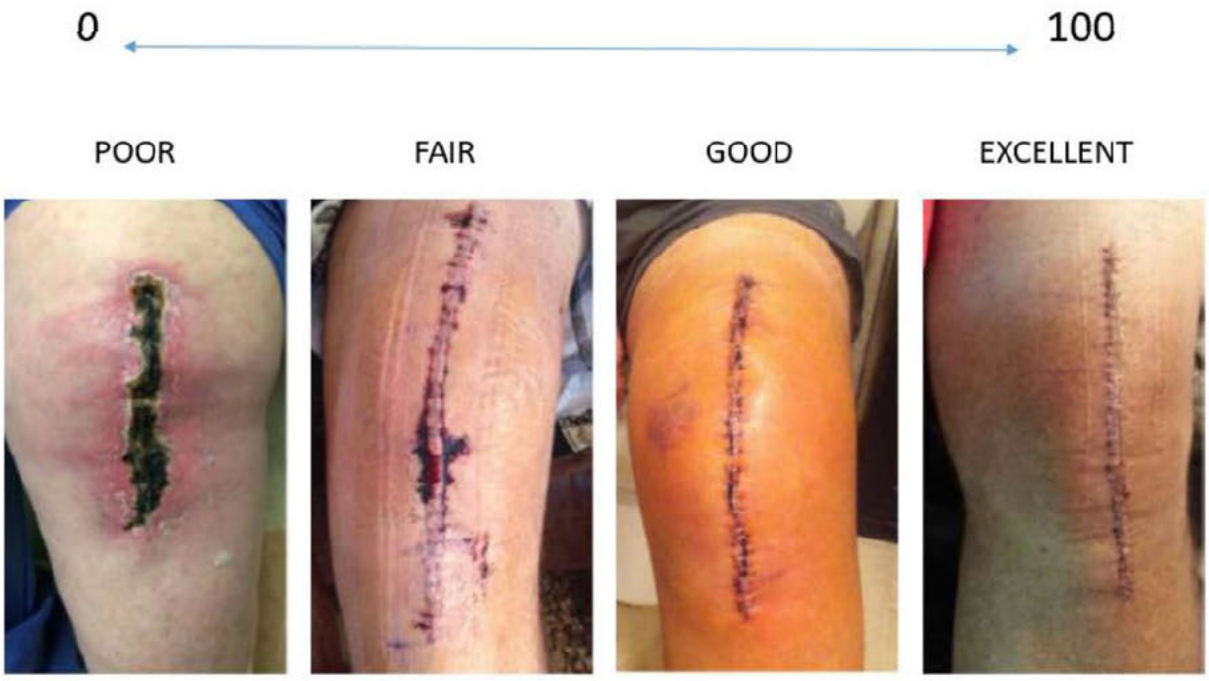


Figure 4 VAS tool for assessment of closed surgical wounds evolution

Results from secondary endpoint assessments (SSC, SSI rates, etc.) will be compared to published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in similar populations to comply with the conditions of MHRA Notice of No Objection (Appendix 23.12). To [redacted] population will closely approximate those of the similar research articles that it will be compared against, the Inclusion and Exclusion criteria have been updated. This allows the risk profile of the [redacted] population to be aligned with the review of literature.

An internal analysis of previously reported level one studies showed the incidence of SSCs in abdominal surgery treated with PICO was 8.2%, (compared to 23.4% in controls). [24,25,39] There is only one study reporting knees alone,[40] with most studies combining both knee and hip arthroplasty, making analysis difficult, and S+N had previously agreed that such studies would not be included. In the study which reported knees alone SSCs were reported in 34% of cases in the PICO group, compared to 77% in the control group.

Results from this trial will be also compared to actually reported rates of SSC in each one of the research centres (where available) for the concerned specialty and types of surgery.

This assessment will be intended to ensure that [redacted] is not compromising subjects' safety and importantly will be a clinical comparison, rather than a statistical comparison.

[redacted]

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

9.2.2 Assessment of peri-wound skin

The skin surrounding the surgical incision will be assessed by the above mentioned clinicians (directly by the treating surgeon) to confirm if the skin appears healthy or is fragile, inflamed, eczematous, dry/flaky, macerated or has erythema, bruising. This assessment will also search for any potential adverse events (e.g. skin irritation, allergy, etc.) on the skin under the [redacted] dressing focusing on the skin [redacted].

In the case of local wound complications inducing local changes like periwound oedema, skin necrosis, dehiscence, [redacted] pictures will be used to assess the evolution of the event until the end of follow-up.

[redacted]® [redacted] Wound Assessment Device allows for a precise determination of surface areas, (depth and volume too if required) thus facilitate an objective follow up of the evolution of skin lesions (erythema, dehiscence).

9.2.3 Assessment of Range of Motion (Phase 1 Only)

Range of motion measurements are not routinely measured in PICO studies, and S&N is not expecting [redacted] to impact negatively the knee Range of Motion (ROM). ROM measurements are included as a requirement from MHRA as part of the safety assessment of the device when used over mobile anatomical regions, i.e. joints. Knee ROM will be assessed using a goniometer by a trained member of the study team (e.g. physiotherapist) at each of the specified time points. It is ideal that only one person is assigned this task for the duration of the study. The assessment will be performed using routine clinical practice to measure flexion and extension of the knee joint.
Results from the ROM measurements were compared to published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in the knee population during the interim analysis.

9.2.4 Photographs and Surgical Site Assessment

Images of the subject's postsurgical incision (and wound zone) will be captured prior to initial dressing application, at 7 days post operatively (or when dressing is removed), at 14 days and at 30 days postoperatively (or early exit visit) using a digital camera supplied by S&N.

Photographic assessment will be performed with the [redacted]® [redacted] [redacted] [redacted]® [redacted] is a portable device that easily allows capture of high-resolution graphic information about a subject's skin wound, which is then managed, analysed and stored in a central database. Information captured includes photographic images, quantitative measures, and other wound assessment data input by the assessing clinician, all obtained with no subject contact. [redacted]® [redacted] builds that information into an electronic record for either printing, electronic uploading to Sponsor's database, further clinical assessment or archiving. Information about performed wound measurements history is available on the system so that progression of the wound status can be calculated and presented.

The images will be used to perform wound assessments by the treating investigator. Photograph should also be taken where appropriate of all DevD reported. Pictures will also constitute the pictorial record of the study reference incisions.

The image should be framed such that the entire incision/dressing area 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 [redacted]® [redacted] camera will be given prior to start of the study.

An image of the dressing in place will be taken after application, and before removal, to check the device compliance. All photographs should be linked to the relevant assessment on the CRF.

[redacted]

[redacted]

[redacted]

[redacted]

9.3 Health Economics/Quality of Life

Specific validated Quality of Life questionnaires will not be collected for this study. However, assessment of acceptability of the therapies will be made by specific targeted questions to the clinician and subject as described in section 9.1.2 above.

10 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.

10.1 General

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 categorical 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. All summaries and analyses will be presented separately for each of the two cohorts of specialties recruited within the study: orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions). No data will be combined between the two specialties.

Primary, secondary, and exploratory outcome variables and derived variables will also be summarised accordingly separately by specialty. 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. The results will be reported at 5% significance level and where appropriate 95% confidence intervals (CI) will be given.

10.2 Analysis Populations

- Safety Population (SAF), including all subjects who have received the study device.
- Full analysis set population (FAS), following ITT principle including all subjects recruited into the study.
- Per-Protocol Population 1 (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 subject populations as follows. Analysis of the primary, secondary and exploratory performance objectives will be performed separately using both the Full Analysis Set and the Per Protocol Population. All safety analyses will utilize the Safety Population, separately for each specialty.

Subsets of the above populations will be used for secondary analyses where appropriate to analyse only those subjects in the abdominal group who were recruited post-interim analysis and followed version 8.0 of the protocol. These subset populations will be labelled with the prefix "s-"so it is clear, for example the subset of the full analysis set will be labelled s-FAS etc.

10.3 Baseline Data

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. For categorical 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.

10.4 Efficacy Analysis

The study is non-comparative and non-randomised, the impact of confounding on the measures of performance may be expected and will be evaluated through descriptive analysis of selected baseline and demographic variables and fitting of appropriate models on selected outcomes presented separately for each specialty.

The primary analysis of the following endpoints will be done using FAS and PP analysis populations. However, an additional analysis will also be carried out on a subset of these populations (s-FAS and s-PP) which includes only subjects who were recruited post-interim analysis and followed protocol version 8.0.

10.4.1 Analysis of Primary Endpoint(s)

- Negative Pressure maintenance at nominal 80mmHg

The following hypotheses will be tested to establish equivalence of the [redacted] compared to the internally derived value, with equivalence margin, $\delta_1>0$, for each specialty cohort:

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 (80.2 mmHg) and μ_0 represents the mean [redacted] operating pressure. The equivalence limit δ_1 = 7mmHg was chosen as a conservative non-clinically significant difference assuming that the difference is actually 0. The hypothesis will be tested by two-one-sided t-test (TOST)

at the alpha level of 0.025 (one-sided), separately for each specialty. If the null hypothesis is rejected, equivalence will be confirmed.

The corresponding 95% CI for each cohort will also be presented.

- Dressing wear time in days as assessed through a combination of data from [redacted] and CRF recorded data of any unplanned dressing change.

The following hypotheses will be tested, for each specialty separately, to establish that the dressing wear time of the [redacted] pump system is strictly no worse (lower) than the literature derived value:

H_0: $\mu - \mu_0 \leq 0$

H_a: $\mu - \mu_0 > 0$

In the stated hypothesis, μ represents the mean [redacted] dressing wear time in days and μ0 represents the literature derived value (4.6 days). A one sided (one sample) t-test with alpha = 0.025 will be used to evaluate the hypothesis for each specialty, the corresponding 95% CIs will also be presented. A binary variable indicating<7 / ≥7 days wear time (denoted by 0/1) will also be used and the proportion of dressings with a wear time≥7 days will be reported as a percentage along with corresponding 95% confidence interval, for each specialty cohort. If necessary and if data allows, important associated factors will be adjusted for in a logistic model.

- Exudate management assessed by no occurrence of exudate leaks as assessed by reported clinical data on any exudate leakage observed through a dressing or around the borders during the dressing wearing period resulting or not, in an unplanned dressing change.

A binary variable for the non-leakage and leakage will be used and the proportion of reported/identified leaks will be presented as a frequency together with a percentage and a

95% CI separately for each specialty. For each specialty, the non-leakage proportion for the study will be tested using the Exact test to establish if it is different from the literature derived value of 85% projected. Further, the resulting lower limit of 95% CI for each specialty will be evaluated to establish if it excludes values of 65% and below.

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

A. Average negative pressure within therapeutic range (-100mmHg to -60mmHg)

B. Dressing wear time is 7 days

C. No exudate leakage

The Composite Clinical Success (CCS) will be reported as a count and percentage with a 95% CI separately for each specialty.

A logistic model will be used to evaluate the adjusted and the un-adjusted models for the CCS primary outcome variable for each specialty, separately. The variables considered important and to be included in the final model are Age, Diabetic status and the presence of any other co-morbidity as a binary variable. All other baseline and medical factors collected at baseline will be evaluated for importance in adjusted models and only those statistically significant in an un-adjusted model will be considered in the final model.

10.4.2 Analysis of Secondary Endpoint(s)

Clinical performance and safety of the [redacted] NPWT system over a 30 day follow-up period will be presented separately for each specialty, and will include**:**

- Incidence of Surgical Site Infection (SSI) – Superficial, deep, organ [CDC criteria] within 30 days of surgery

- Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep, partial/total), seroma, necrosis, hematoma, suture abscess] within 30 days of surgery
- Wound and Skin VAS score assessment at 7, 14 and 30 days
- Condition of peri-wound skin and skin under the pump [redacted] assessed through visual inspection at 7, 14 and 30 days.
- Level of pain during wear of the [redacted] system, and at dressing removal assessed by VAS scale following 7-day therapy
- Phase 1 only: Comparison of Wound and Skin VAS scores at days 7, 14 and 30 as assessed by the treating clinicians versus scores provided by the independent assessor.
- Phase 1 only: Range of motion assessment (ROM) for the knee at pre-operative visit, post-operative visit, 7, 14 and 30 days.
- Level of pain during dressing removal (VAS scale) - pain intensity as none, mild, moderate, or severe.

For incidence of SSI and incidence of SSC binary variables indicating presence of/absence of will be defined and the frequencies together with percentages reported/identified outcomes will be reported separately for each specialty. A logistic model will be used to evaluate the adjusted and the un-adjusted models for the secondary variables, the incidence of surgical site infections, and incidence of surgical complications separately for each specialty. The variables considered important and to be included in the final model are Age, Diabetic status and the presence of any other co-morbidity as a binary variable. All other baseline and medical factors collected at baseline will be evaluated for importance in adjusted models and only those statistically significant in an un-adjusted model will be considered in the final model.

Where the data is recorded both by the treating investigator, and by an independent medically qualified individual/assessor (for example, the wound and skin VAS score), the assessments will be presented separately for each assessor and results cross-tabulated

between assessors where appropriate. In each case analyses will be presented separately for each specialty.

Summary statistics for all other secondary variables will be given, for each specialty separately, according to the nature of the variable, continuous or categorical. For categorical 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. 95% confidence intervals will be reported where appropriate.

As range of motion is collected for subjects in the knee surgery group only there will be no summary of ROM in the s-FAS and s-PP analysis.

10.4.3 Analysis of Exploratory Endpoints

- Acceptability (clinician/subject questionnaires)
- Subject comfort during wear (subject questionnaire)
- Ease of application & removal

All exploratory end points will be summarised through descriptive statistics and tabulated accordingly, separately for each specialty. For categorical 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. 95% confidence intervals will be reported where appropriate.

10.5 Safety Analyses

- Adverse Events and Device Deficiencies

All safety analyses and summaries will be conducted using the Safety Population. All safety summaries will be presented by specialty in conjunction with selected demographic variables e.g. gender.

10.6 Interim Analyses

As a condition for the MHRA No Objection decision, an interim analysis was required to be performed once the study has recruited 22 subjects in each specialty group who had completed the follow-up period. The study was paused while the MHRA assessed the results.

There will be no further interim analysis performed as part of Phase 2 of this study.

11 SAMPLE SIZE JUSTIFICATION

11.1 Sample Size Justification Pre-Interim Analysis

The sample size is justified based on the proposed three primary outcome variables of nominal pressure of 80mmHg, Dressing wear time in days and exudate management based

on incidence of exudate leakage. Each of the three hypotheses will be tested separately for each specialty cohort.

For the nominal pressure the sample size is based on analysis to test equivalence of negative pressure delivery against the reference value of 80.2mmHg. Previous data extracted from the PICO 7 system were found to be distributed with a SD=14.8. For purposes of sample size calculation, the a priori assumption is that the [redacted] system will have a similar operating pressure to PICO 7, and therefore similar variability in pressure delivery is assumed. The following hypotheses will be tested to establish the equivalence in mean operating pressure of [redacted] system over 7 days compared to the reference value for PICO 7 (80.2 mmHg) with equivalence margin, $\delta 1$:

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

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

In the stated hypotheses, μ represents the mean operating pressure of [redacted] system and μ_0 represents , the reference value relating to the mean operating pressure of PICO 7 (=80.2mmHg, SD=14.8). The equivalence margin, $\delta 1$ = 7 mmHg was chosen as a conservative non-clinically significant difference for operating pressure assuming the difference is actually 0. The hypothesis will be tested, separately for each specialty cohort by a two-sided t-test (TOST) at the alpha level of 0.025 (one-sided). If the null hypothesis is rejected, clinical equivalence in terms of pressure delivery will be confirmed.

Based on the data used for sample size estimation, thirty eight (38) subjects are required to achieve 80% power to detect equivalence at the significance level of α = 0.025 (one-sided) within 7mmHg using a two-sided t-test. Drawing from past experience, allowing that 15% of the subjects may be lost to follow up by the end of the study, a sample size of 44 subjects

per specialty are needed to achieve sufficient statistical power for each specialty to be analysed separately, within this study.

Based on the above, a total of 88 subjects will be recruited, which will include 44 subjects with each of the following specialties: orthopaedics (closed surgical knee incisions, e.g. after total knee arthroplasty), and abdominal surgery (e.g. closed surgical abdominal incisions of which at least 50% would be colorectal cases).

For the management of exudate, measured by incidence of exudate leakage, the sample size is evaluated for adequacy based on the non-leakage rate recorded by the NWPT system. According to internal data collected within Smith and Nephew surgical study involving Closed Abdominal and Orthopaedic subjects, 85% of the PICO NPWT systems had no exudate leaks. Therefore, assuming that [redacted] NWPT system will manage 85% of exudate effectively or better, demonstrated through no exudate leakage observed, a sample size of 10 subjects for each specialty will be sufficient to exclude a response rate of 65% or less with 80% power by using a 2-sided 95% confidence interval for orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions) separately. With the planned 44 subjects per specialty, a response rate below 70% could be excluded for each specialty individually.

For the dressing wear time (in days) the sample size is based on comparison of the [redacted] system compared to the literature derived value for each specialty separately. The mean dressing wear time derived from literature is 4.6 days and a standard deviation of 2.2539. It is projected that the [redacted] NWPT system will have a mean dressing wear time of 7 days with similar distribution to the literature value.

The following hypotheses will be tested, for each specialty separately, to establish that the dressing wear time of the [redacted] system is strictly not worse (lower) than the literature derived value:

H_0: $\mu - \mu_0 \leq 0$

H_a: $\mu - \mu_0 > 0$

In the stated hypothesis, μ the mean [redacted] pump dressing wear time and μ0 represents the literature derived value (4.6 days). A one-sided (one sample) t-test with alpha = 0.025 will be used to evaluate the hypothesis for each specialty. Based on the expected mean dressing wear time of 7 days, literature derived value of 4.6 days, and a standard deviation of 2.25 days, 80% power and 2.5% significance level, a sample size of 10 subjects per specialty is adequate to perform the above the hypothesis separately for each specialty cohort. Therefore, the planned forty-four subjects per specialty cohort are adequate to conclude that the [redacted] [redacted] system is strictly not worse (lower) than the literature derived value for each speciality individually. Further, with the planned 44 subjects per specialty, a dressing wear time below 6.0 days could be excluded for each specialty individually for the [redacted] device, represented by the lower limit of the 95% confidence interval lying above 6.0 days, based on assumptions previously listed; one-sided t-test with 80% power, 2.5% significance level, with a standard deviation of 2.25 days and assumed 7 day wear time of the [redacted] device.

No adjustment to the sample size calculations will be made to account for interim report related to safety review. The sample size was estimated using nQuery Advisor 4.0 and statistical software SAS Version 9.4.

11.2 Changes to Sample Size Post-Interim Analysis

An interim analysis was done after 44 subjects were recruited (22 from each indication). Based on the root cause analysis of seal loss, the study will continue on Abdominal surgical indications only at this time, whilst further investigative work continues into understanding the cause of seal loss in the orthopaedic surgery group.

The 2nd phase of the study (post-interim analysis) will be powered according to previous sample size. However, as no further subjects will be recruited for the orthopaedic surgery group, all 44 subjects recruited will be in the abdominal indication group. This will increase the total number of abdominal incisions to 66 (22 recruited following the protocol v7.0 and 44 following v8.0 of the protocol). This ensures that the primary endpoint is sufficiently powered for both the primary analysis of the abdominal data for all subjects as well as for a secondary analysis to be done on the data from those recruited according to protocol v8.0 only.

12 ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 Definitions (ISO/DIS 14155)

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

Table 1 Categories of Adverse Events

	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 to entry: This definition includes events related to the investigational medical device or the comparator.
Note 2 to entry: This definition includes events related to the procedures involved.
Note 3 to entry: For users or other persons, this definition is restricted to events related to 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 to entry: 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 to entry: 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 disease, 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 (DevD) 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

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

12.3 Reporting procedures

AE of any kind and DevD 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 6 and 7):

- 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 timescales above.

All AEs and DevDs 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 according to the IRB/IEC requirements.

MHRA Reporting

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.

In addition to the reporting of individual serious adverse events as detailed above, a quarterly summary report of all serious adverse events will be provided to MHRA.

Reporting to EC

A SAE occurring to a research participant should be reported to the Committee where in the opinion of the Chief Investigator the event was related to administration of any of the research procedures, and was an unexpected occurrence.

Reports of SAEs should be provided to the REC within 15 days of the Chief Investigator becoming aware of the event, in the format prescribed by the HRA and published on the website:

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, ADE and SADE, unanticipated SADE, and DD.

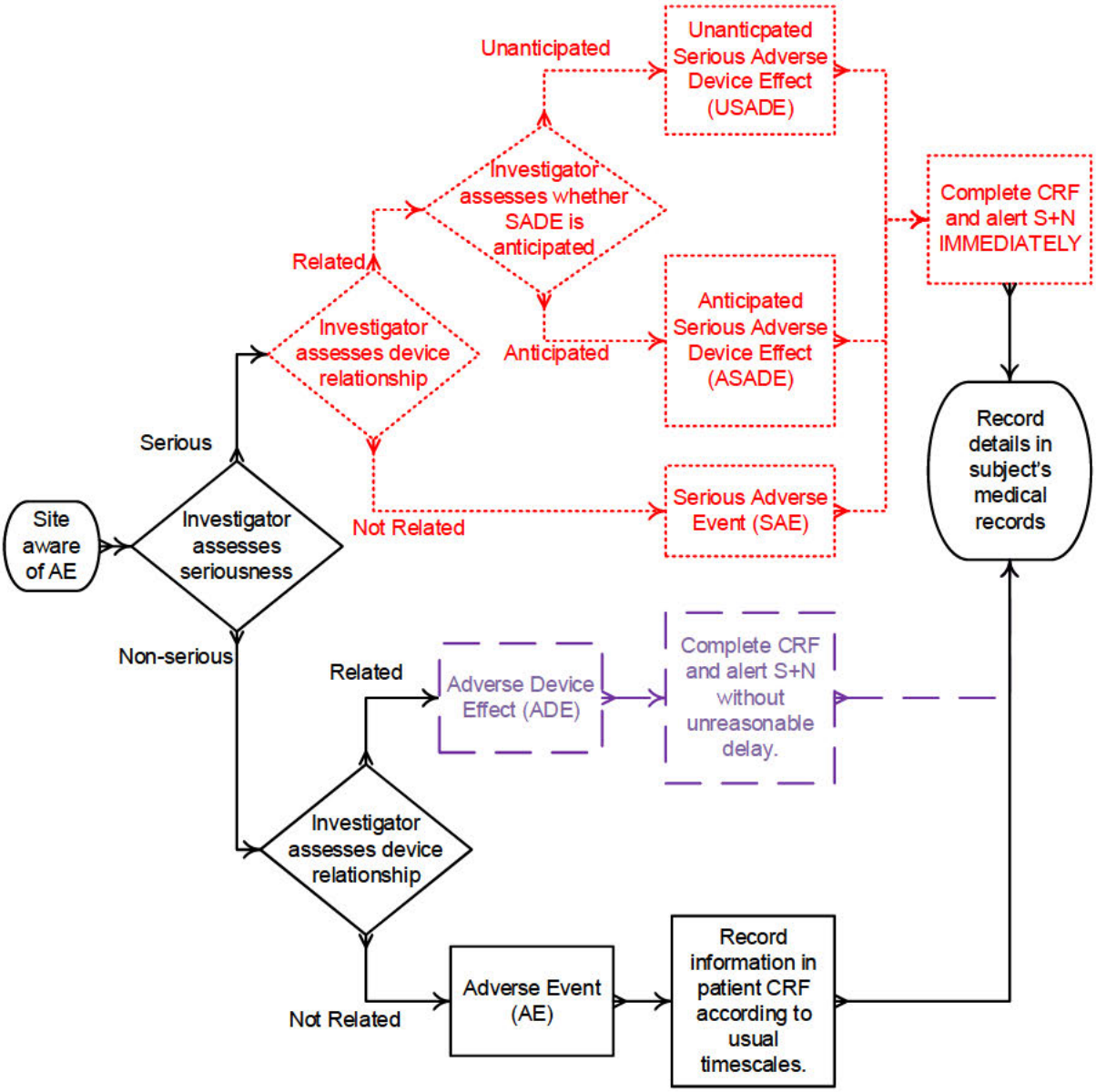


Figure 5 Evaluation and Reporting of AE

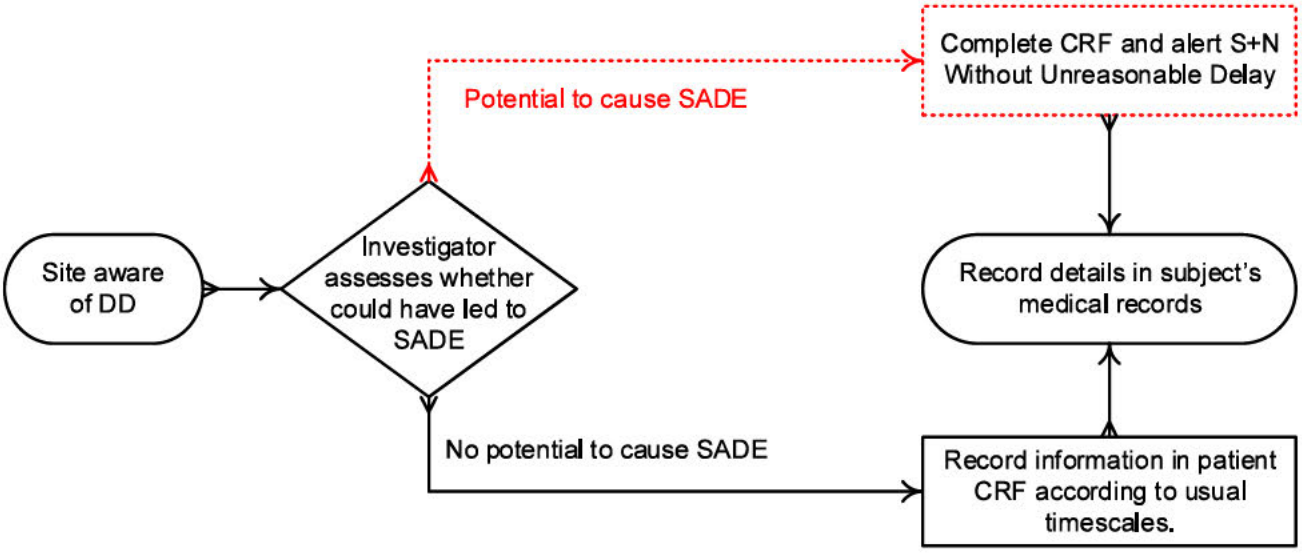


Figure 6 Evaluation and Reporting of DD

12.4 Unblinding of Investigational Product

This is not applicable as the study is not blinded.

12.5 Follow-up of Subjects with Adverse Events

For subjects who are experiencing ongoing unresolved AE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit in order 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 within the CRF and Clinical Study Report.

12.5.1 Ongoing Adverse Events at Study Discontinuation

Adverse events which are **related** to a study procedure or S+N IP and are ongoing at end of subject's participation 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 end of subject's participation should be followed for 30 days after discontinuation in the study, or until the AE is resolved, whichever is sooner.

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

13 INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with the commitments outlined in the 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 22.11 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.

14 SPONSOR AND MONITOR RESPONSIBILITIES

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that: the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from

the source documents; and the study is conducted in compliance with the currently approved protocol and amendment(s), if applicable, with GCP regulations, and with applicable regulatory requirements.

For this study there will be 100% source data verification on all variables which will be verified from the eCRF against subject medical records or source note worksheets or a combination of these documents. Detailed monitoring requirements will be documented within the Clinical Monitoring Plan for this study.

14.1 Contract Research Organisation

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

14.2 Site Qualification Visit

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

14.3 Site Initiation Visit

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

14.4 Interim Monitoring Visit

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

14.5 Sponsor Audits and Regulatory Inspection

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

14.6 Close-Out Visit

Study close-out visits 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 remove close-out visit may be conducted.

15 PROTOCOL DEVIATIONS

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Protocol deviations reported by the Investigator or discovered during monitoring visits will be compiled in a Protocol / GCP Deviation Log (TMP-CD-31-02 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (TMP-CD-31-01 Protocol/GCP Deviation) including identified root cause and, as necessary, appropriate corrective and preventive actions will be put in place and signed off by the study personnel. If it is deemed necessary full clinical CAPA will be initiated.

It is not allowed to use waivers to allow planned deviation of the study protocol.

An investigator may be early terminated from the study upon identification of serious protocol deviations whereby there are concerns for patient safety or data quality (especially those not reported to the sponsor by the site). Early termination may also occur if there are repeated protocol deviations which have previously been addressed via corrective and preventative actions thereby suggesting an issue with site compliance.

Give notification requirements and timeframes here for site staff and monitor to report to S+N and PI to report to IRB/IEC (which may be conducted by CSM).

16 PROTOCOL AMENDMENTS

Amendments should be made only in exceptional cases once the study has started. Protocol amendments must be approved by the protocol signatories prior to submission to the 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.

17 CONFIDENTIALITY OF THE STUDY

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

18 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/favourable opinion from the IRB/IEC and regulatory authority has been obtained. Any additional requirements imposed by the IRB/IEC or regulatory authority will be followed.

Public 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.

19 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 18 months. This includes an estimated six-month pause in enrolment while the interim analysis is reported to the MHRA. The length may be extended by the actual length of interim analysis review. 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 complication).

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.

20 PUBLICATION POLICY

20.1 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.

20.2 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 9 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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22 APPENDICES

22.1 Protocol Amendment 9

22.1.1 General Purpose

This amendment has been completed to document a clarification and update to Inclusion/Exclusion criteria, secondary endpoint and include the regulatory need being met by this study.

22.1.2 Rationale

Updates to the protocol were made to expand the inclusion criteria to include gynaecologic procedures, as this is a common abdominal surgery, which can occur alongside gastrointestinal surgical procedures and results in a closed surgical incisions; the indication under investigation within this study. The exclusion criteria for laparoscopic surgeries was also clarified to remove the focus on surgical incision technique and specify that the procedure requires an incision that must be greater than or equal to 5 cm to be eligible for study inclusion. This is regardless of how the incision is created, which has been clarified and stated within the inclusion criteria, number 7. In addition, the changes agreed with MHRA for the continuation of this study which was missed in the last protocol version (retain only evaluation of VAS wound scores by treating clinician for phase 2) was added in this current version as well as wording to highlight the regulatory need being met by this study. A discussion on use of portable negative pressure in wound healing was deleted in error in the last version of this protocol and is being reinstated in this version.

22.1.3 Effect on Study Procedures

This amendment expands the patient population for the study to include gynaecologic procedures. This will be applied following amendment 9 approval. Amendment 9 also clarifies the definition for an appropriate/eligible incision in patients undergoing laparoscopic procedures (whereby an extended trocar port site of greater than or equal to 5cm has always been eligible in addition to a midline laparotomy) which should apply to the full study. This simplified language, therefore, removes the double negative wording within the exclusion criteria (number 13) of Amendment 8 and consolidates all procedural eligibility within the inclusion criteria, under inclusion number 7.

22.1.4 Details

Section	Revised Text 12/MAR/2021 Version 8	Revised Text 04/AUG/2021 Version 9
2 Synopsis Inclusion Criteria	In Abdominal surgery: subject is scheduled for an elective open gastrointestinal surgery and has an ASA score of 2-3	In Abdominal surgery: subject is scheduled for an elective open or laparoscopic gastrointestinal and/or gynaecological surgery with incision ≥5cm and has an ASA score of 2-3.
2 Synopsis Exclusion Criteria	Subjects undergoing exclusively abdominal laparoscopic surgery (except if the procedure is scheduled to include a laparotomy incision ≥ 5 cm.	
4.1.2	The cost of wound healing failures and complications *(duplicate of 4.1.1, copied in error when protocol v7 was moved to a new template deleting the discussion on use of portable negative pressure in wound healing)*	Use of portable negative pressure in wound healing *(reinstated from v7.0)*
4.3 Study Purpose	There is a need to generate clinical evidence for the [redacted] NPWT system to demonstrate safety and performance of the device.	The study results will be used to generate data to support regulatory submission for CE marking. There is a need to generate clinical evidence for the [redacted] NPWT system to demonstrate safety and performance of the device.
7.2 Inclusion Criteria	In Abdominal surgery: subject is scheduled for an elective open gastrointestinal surgery and has an ASA score of 2-3	In Abdominal surgery: subject is scheduled for an elective open or laparoscopic gastrointestinal and/or gynaecological surgery with

		incision >/=5cm and has an ASA score of 2-3.
7.3 Exclusion Criteria	Subjects undergoing exclusively abdominal laparoscopic surgery (except if the procedure is scheduled to include a laparotomy incision ≥ 5 cm.	
8.4.2 Secondary Endpoints	Comparison of Wound and Skin VAS scores at days 7, 14 and 30 as assessed by the treating clinicians versus scores provided by the independent assessor.	Phase 1 only: Comparison of Wound and Skin VAS scores at days 7, 14 and 30 as assessed by the treating clinicians versus scores provided by the independent assessor.
10.4.2 Analysis of Secondary Endpoints	Comparison of Wound and Skin VAS scores at days 7, 14 and 30 as assessed by the treating clinicians versus scores provided by the independent assessor.	Phase 1 only: Comparison of Wound and Skin VAS scores at days 7, 14 and 30 as assessed by the treating clinicians versus scores provided by the independent assessor.

22.1.5 Approvals/Notifications

These updates are considered a substantial amendment and will be notified to MHRA and submitted for EC approval. The changes will only be implemented after MHRA/EC approval confirmation.

22.2 Protocol Amendment 8

22.2.1 General Purpose

This amendment has been completed to document changes as agreed with MHRA following interim analysis discussion.

22.2.2 Rationale

Updates to the protocol have been made to:

- Reflect the changes agreed with MHRA to allow for Phase 2 recruitment to continue
- Up-version to rebranded protocol template

22.2.3 Effect on Study Status

Not applicable; this amendment is to be in effect and implemented prior to subject enrollment for Phase 2.

22.2.4 Details

Section	Current Text 10/APR/2019 Version 7	Revised Text 12/MAR/2021 Version 8
Header	Old branding: smith&nephew	New branding: Smith+Nephew
Footer	[redacted]	[redacted]
1 Signatures	I have read the attached protocol entitled "[redacted] Pre-Registration Clinical Study", version 7.0, dated 10APR2019	I have read the attached protocol entitled "[redacted] Pre-Registration Clinical Study", version 8.0, dated 12/MAR/2021 Signature page updated with name of current approvers
2 Synopsis Sample Size	A total of 88 subjects will be recruited to allow for 44 subjects to be recruited from each of the following specialties: orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical	It was planned to recruit a total of 88 subjects to allow for 44 subjects to be recruited from each of the following specialties: orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed

	incisions of which at least 50% would be colorectal cases).	abdominal surgical incisions of which at least 50% would be colorectal cases). An interim analysis was made after 44 subjects were recruited (22 from each indication). Based on the root cause analysis of seal loss, the study will continue on Abdominal surgical indications only at this time, whilst further investigative work continues into understanding the cause of seal loss in the orthopaedic surgery group. The 2nd phase of the study (post-interim analysis) will be powered according to previous sample size. However, as no further subjects will be recruited for the orthopaedic surgery group, all 44 subjects recruited will be in the abdominal indication group. This will increase the total number of abdominal incisions to 66 (22 recruited following the protocol v7.0 and 44 following v8.0 of the protocol). This ensures that the primary endpoint is sufficiently powered for both the primary analysis of the abdominal data for all subjects as well as for a secondary analysis to be done on the data from those recruited according to protocol v8.0 only.
2 Synopsis Number of Study Sites	Up to 6 total (three sites for each of the specialties)	There were 6 sites involved in the first phase of recruitment (three sites for each of the specialties). Based on the interim analysis, the study will continue on abdominal surgical indications

		only with 6 sites for the second phase of recruitment.
2 Synopsis Targeted Global Regions	UK and EU	UK
2 Synopsis Inclusion Criteria	• In Orthopaedic surgery: subject is scheduled for an elective primary knee replacement arthroplasty and ASA score of 2-3	• *(Phase 1 only)*: In Orthopaedic surgery: subject is scheduled for an elective primary knee replacement arthroplasty and ASA* score of 2-3.
2 Synopsis Exclusion Criteria		Added new exclusion criteria: 15. Subjects where the dressing cannot be fully applied without coming into contact with, or covering, tubes, drains, wires or other ancillary devices which may affect the seal, and/ or which will require removal before the end of the seven day period"
2 Synopsis Study Duration	Eighteen months from when the first study site is initiated until last enrolled subject reaches last study assessment. This period includes an estimated 6 month period to prepare a mid-recruitment interim report, submit it and obtain feedback from MHRA.	Prior to the interim analysis, it was estimated that the study duration will be eighteen months from when the first study site is initiated until last enrolled subject reaches last study assessment. This period included an estimated 6 month period to prepare a mid-recruitment interim report, submit it and obtain feedback from MHRA. To reflect the much longer pause taken and time to secure approvals, the study duration is now expected to last 30 months.
2 Synopsis	Exudate management assessed by no occurrence of exudate	Exudate management assessed by no occurrence of exudate

Primary Endpoint	leaks as assessed through a combination of leakage alert data from device [redacted] and/or clinical data on any leakage observed during the dressing wearing period resulting or not, in an unplanned dressing change	leaks as assessed through clinical data on any leakage of exudate through a dressing or around the borders observed during the dressing wearing period resulting or not, in an unplanned dressing change
2 Synopsis Secondary Endpoints	• Range of motion assessment (ROM) for the knee at pre-operative visit, post-operative visit, 1, 7, 14 and 30 days.	• *(Phase 1 only)* Range of motion assessment (ROM) for the knee at pre-operative visit, post-operative visit, 1, 7, 14 and 30 days.
2 Synopsis Study Schedule	Study Window: End of Therapy Assessment 7 (±1) day	Study Window: End of Therapy Assessment 7 days
2 Synopsis Study Schematic	Range of motion assessment*,** *Post dressing application **Pre and post-dressing removal	*(Phase 1 only)* Range of motion assessment*,** *Post dressing application **Pre and post-dressing removal
Table of Contents		Updated to reflect changes
4.4 Safety Considerations	Precautions: • [redacted] may be used in conjunction with surgical drains provided the dressing is 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. RENASYS Gel patches can be employed in awkward areas as a means to achieve a seal.	Precautions: • [redacted] may be used in conjunction with ancillary devices such as surgical drains, PICC lines and other dressings, however these products should not be used under the [redacted] dressing or dressing border as these products may cause air leaks into the dressing. RENASYS Gel patches can be employed in awkward areas as a means to achieve a seal.

4.4 Safety Considerations	**Storage** The [redacted] system must be stored between 5 and 25°C.	**Storage** The [redacted] system must be stored between 5 and 25°C and relative humidity between 10-75%.
5.2 Secondary Objectives	Range of motion assessment (ROM) for the knee	*Phase 1 only:* Range of motion assessment (ROM) for the knee
6. 1.1 Investigational Product	For this study, [redacted] system will be used to manage surgically closed incision sites (abdominal and knee).	For this study, [redacted] system will be used to manage surgically closed incision sites (abdominal and knee [phase 1 only]).
6.2.1 Investigational Product		Added instructions on Dressing Application:
	1. Remove any excess hair. Flush out the wound with saline solution and pat dry any excess moisture.	1. Remove any excess hair during surgical preparation. Clean the skin surrounding the incision with saline solution and pat dry any excess moisture. 2. Plan the placement of the dressing over the surgical incision. Ensure there is enough clearance such that the edges of the dressing (including the adhesive strips once applied) would not overlap any ancillaries such as stomas, catheter lines, drains, dressings over smaller incisions etc. that will need to be adjusted or removed before the end of the treatment period of 7 days.
	4. Apply the absorbent part of the dressing centrally over the top of the wound. [redacted]	4. Apply the absorbent part of the dressing centrally over the top of the incision. [redacted]

	[redacted] over the wound.	[redacted] over the incision.
6.2.1.3 Securing [redacted] in place	6. Apply a fixation strip along each edge of [redacted] using the same technique described in steps 11 to 15 to achieve a good seal.	6. Apply a fixation strip along each edge of [redacted] using the same technique described in steps 11 to 15 to achieve a good seal, ensuring that they do not overlap any ancillary devices such as drains, wires etc.
6.3 packaging and Labelling	Packaging and labelling will be prepared to meet regulatory requirements.	Packaging and labelling will be prepared to meet regulatory requirements. Package integrity and labelling should be verified prior to use of the product and confirmed in the CRF.
7.1 Subject Population	Approximately 88 subjects scheduled for abdominal or knee surgery will be recruited to the study and will receive [redacted] The subjects will be recruited from up to 6 sites in the United Kingdom and EU. Sites failing to enrol may be replaced. There will 44 subjects recruited per surgical group (abdominal, knee) and 3 research sites per surgical specialty.	The original plan was to recruit a total of 88 subjects to allow for 44 subjects to be recruited from each of the following specialties: orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions of which at least 50% would be colorectal cases). There were 6 sites involved in the first phase of recruitment (three sites for each of the specialties). An interim analysis was made after 44 subjects were recruited (22 from each indication). Based on the root cause analysis of seal loss, Phase 2 of the study will

		continue on Abdominal surgical indications only at this time, whilst further investigative work continues into understanding the cause of seal loss in the orthopaedic surgery group. The 2nd phase of the study (post-interim analysis) will be powered according to previous sample size. However, as no further subjects will be recruited for the orthopaedic surgery group, all 44 subjects recruited will be in the abdominal indication group.
7.2 Inclusion Criteria	• In Orthopaedic surgery: subject is scheduled for an elective primary knee replacement arthroplasty and ASA score of 2-3	• *(Phase 1 only)*: In Orthopaedic surgery: subject is scheduled for an elective primary knee replacement arthroplasty and ASA* score of 2-3.
7.3 Exclusion Criteria		Added new exclusion criteria: Subjects where the dressing cannot be fully applied without coming into contact with, or covering, tubes, drains, wires or other ancillary devices which may affect the seal, and/ or which will require removal before the end of the seven day period
7.5 Informed Consent	All subjects will be given ample time (at least 24 hours) to consider participation following the explanation of the study/reading of the patient information sheet.	All subjects will be given ample time (at least 24 hours) to consider participation following the explanation of the study/reading of the patient information sheet.

		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.
7.8.1 Withdrawal from Treatment	• 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 prematurely ended for any reason (i.e. due to removal of the system by the subject or the investigator, failure of the pump, dressing falls off, seal can no longer be established)
8.1 Study Design	This study is a prospective, multi-centre, non-randomised, non-blinded, single arm follow-up study to assess clinical performance and safety of [redacted] It is anticipated that up to 6 sites will participate within the UK and EU.	This study is a prospective, multi-centre, non-randomised, non-blinded, single arm follow-up study to assess clinical performance and safety of [redacted] It is anticipated that up to 6 sites will participate within the UK.
8.3 Data Management	V7.0 did not have a data management section	**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.

8.3.1 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. **8.3.2 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.
8.4.1 Primary Endpoint	• Exudate management assessed by no occurrence of exudate leaks as assessed through a combination of leakage alert data from the device [redacted] and/or clinical data on any leakage observed during the dressing wearing period resulting or not, in an unplanned dressing change.	• Exudate management assessed by no occurrence of exudate leaks as assessed through clinical data on any leakage of exudate through a dressing or around the borders observed during the dressing wearing period resulting or not, in an unplanned dressing change.
8.4.2	• Range of motion assessment (for knee subjects only) at pre-	• *(Phase 1 only):*Range of motion assessment (for knee

	operative, post-operative day 1, 7, 14 and 30 days	subjects only) at pre-operative, post-operative day 1, 7, 14 and 30 days
8.5.3	The study included a single indication in two different surgical specialties and a range of contoured areas of the body where it may be difficult to obtain an effective negative pressure seal and where there may be a range of motion throughout therapy (i.e. knee). The inclusion/exclusion criteria are also not too restrictive with regard to subject demographic. This should mean that the results will be representative of a real clinical setting in hospital or at home, and for the proposed indication in the two specialties.	Phase 1 of the study included a single indication in two different surgical specialties and a range of contoured areas of the body where it may be difficult to obtain an effective negative pressure seal and where there may be a range of motion throughout therapy (i.e. knee). The inclusion/exclusion criteria are also not too restrictive with regard to subject demographic. This should mean that the results will be representative of a real clinical setting in hospital or at home, and for the proposed indication in the two specialties.
9.1.1 Study Procedures by Visit	Study Window: End of Therapy Assessment 7 (±1) day	Study Window: End of Therapy Assessment 7 days
9.1.1 Study Procedures by Visit	Range of motion assessmentl	Range of motion assessment (phase 1 only)
9.1.2 Screening/Preoperative Visit	4. Obtain range of motion measurements (knee subjects only)	4.Obtain range of motion measurements (for knee subjects only in Phase 1)
9.1.3 Baseline Operative Visit	8. Dispense study product. Record pump lot number, size of dressing used ([redacted] and any ancillary products applied (SECURA No-	8. Dispense study product. Record pump lot number, size of dressing used ([redacted]) and any ancillary products applied (SECURA No-Sting Skin prep, RENASYS

	Sting Skin prep, RENASYS Adhesive Gel Patch).	Adhesive Gel Patch). Include also ancillaries in the vicinity (e.g. drains, stomas, lines, dressings).
9.1.3 Baseline Operative Visit	10. Take photograph of dressing in place.	10. Take photograph of dressing in place. Take a photograph of the carton label to aid accountability checks (the label will contain the batch number).
9.1.4 Baseline Post-Operative visit	3. Obtain range of motion measurements (knee subjects only)	3. Obtain range of motion measurements (for knee subjects only in Phase 1)
9.1.6 End of Therapy Assessment	7. Obtain range of motion measurements (knee subjects only)	7. Obtain range of motion measurements (for knee subjects only in Phase 1)
9.1.6 End of Therapy Assessment	14. Assess the surrounding skin including the area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)	13. Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated) 14. Assess the skin area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)
9.1.6 End of Therapy Assessment	15. Obtain range of motion measurements (knee subjects only)	Obtain range of motion measurements (for knee subjects only in Phase 1)
9.1.7 Day 14	4. Assess the surrounding skin including the area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)	4. Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated) 5. Assess the skin area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)

9.1.7 Day 14	5. Obtain range of motion measurements (knee subjects only)	6. Obtain range of motion measurements (for knee subjects only in Phase 1)
9.1.8 Day 30	4. Assess the surrounding skin including the area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)	4. Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated) 5. Assess the skin area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated)
9.1.8 Day 30	5. Obtain range of motion measurements (knee subjects only)	6. Obtain range of motion measurements (for knee subjects only in Phase 1)
9.1.10 Concomitant Therapies	• No dressings (i.e. foam, gauze, ACTICOAT) should be used under the IP during therapy.	• No dressings (i.e. foam, gauze, ACTICOAT, wound contact layers) should be used under the IP during therapy.
9.2.1 Incision Closure, SSC and CDC-SSI incision assessment	In addition, 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 a photographic incision assessment. This will include 1) assessment of whether the incision is fully closed/epithelialised, 2) assessment of infection, dehiscence or other complications. 3) Assessment of any potential AE on the skin under the dressing, and particularly the skin under the pump. 4) Wound assessment	Deleted section

	using the validated 100 mm VAS scoring tool. This assessment will use pictures captured with [redacted] ® [redacted] The independent expert will be blinded to time points.	
9.2.1 Incision Closure, SSC and CDC-SSI incision assessment	Results from secondary endpoint assessments (SSC, SSI rates, etc.) will be compared to published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in similar populations to comply with the conditions of MHRA Notice of No Objection (Appendix 23.12). To ensure [redacted] population will closely approximate those of the similar research articles that it will be compared against, the Inclusion and Exclusion criteria have been updated. This allows the risk profile of the [redacted] population to be aligned with the review of literature. The additional published papers on similar populations will be identified prior to start inclusion. Data comparison will be part of the interim analysis report, which is planned as described in section 10.6. As this data comparison will be based on secondary endpoints, it will be intended mainly to explore the potential of [redacted] to safely promote clinical benefits.	Results from secondary endpoint assessments (SSC, SSI rates, etc.) will be compared to published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in similar populations to comply with the conditions of MHRA Notice of No Objection (Appendix 23.12). To ensure [redacted] population will closely approximate those of the similar research articles that it will be compared against, the Inclusion and Exclusion criteria have been updated. This allows the risk profile of the [redacted] population to be aligned with the review of literature. An internal analysis of previously reported level one studies showed the incidence of SSCs in abdominal surgery treated with PICO was 8.2%, (compared to 23.4% in controls). [24,25,39] There is only one study reporting knees alone,[40] with most studies combining both knee and hip arthroplasty, making analysis difficult, and S+N had previously agreed that such studies would not be included. In the study

Relevant published information for this purpose include so far the following:
Karlakki et al [2016][17] reported a combined rate of SSC of 8.4% in 107 subjects treated with standard dressings (63 hips and 44 knees). If taken separately, the rate of SSC was 13.6% after TKA and 4.7% after THA. Complications included: superficial wound infections, haematoma, and prolonged wound discharge.

Pellino et al. [2014][24] reported in a cohort of 25 colorectal subjects, after abdominal surgery, a length of stay of 7.1 days, a rate of seroma of 40%, and a SSI rate of 44% according to CDC criteria.

O'Leary et al [2016][30] found a SSI rate of 32% after 30 days follow up in a cohort of 25 subjects, whose closed abdominal incision was treated with standard dressings after undergoing open abdominal surgery. Length of stay for this group was 14.7 days.
A summary of this relevant evidence for the surgical incision proposed in this protocol is presented in Table 9.2.1.1

Table 9.2.1.1 Rates of surgical site complications as reported in relevant scientific papers

which reported knees alone SSCs were reported in 34% of cases in the PICO group, compared to 77% in the control group.

Reference	Incision type	Reported rate of SSC, (size of cohort) with Standard Dressings
Karlakki et al [17]	Closed surgical knee incision	13.6% (n=44)
Pellino et al [24]	Closed surgical abdominal incision (colorectal subjects only)	SSI at 30 days 44% (n=25)
O'Leary et al [30]	Closed surgical abdominal incision	SSI at 30 days 32% (n=25)

9.2.2 Assessment of Peri-wound skin	The skin surrounding the surgical incision will be assessed by the above mentioned clinicians (directly by the treating surgeon and pictorially by the independent expert) to confirm if the skin appears healthy or is fragile, inflamed, eczematous, dry/flaky, macerated or has erythema,	The skin surrounding the surgical incision will be assessed by the above mentioned clinicians (directly by the treating surgeon) to confirm if the skin appears healthy or is fragile, inflamed, eczematous, dry/flaky, macerated or has erythema,
9.2.3 Assessment of ROM	Assessment of Range of Motion	Assessment of Range of Motion (Phase 1 only)
9.2.4 Photographs and Surgical Site Assessment	9.2.4 Photographs and Surgical Site Assessment The images will be used to perform wound assessments by the treating investigator and by an independent expert.	9.2.4 Photographs and Surgical Site Assessment The images will be used to perform wound assessments by the treating investigator.

[redacted]

10.2 Analysis Populations	• Full analysis set population (FAS), including all subjects recruited into the study. 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.	• Safety Population (SAF), including all subjects who have received the study device. • Full analysis set population (FAS), following ITT principle including all subjects recruited into the study. • Per-Protocol Population 1 (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 subject populations as follows. Analysis of the primary, secondary and exploratory performance objectives will be performed separately using both the Full Analysis Set and the Per Protocol Population. All safety analyses will utilize the Safety Population, separately for each specialty.

		Subsets of the above populations will be used for secondary analyses where appropriate to analyse only those subjects in the abdominal group who were recruited post-interim analysis and followed version 8.0 of the protocol. These subset populations will be labelled with the prefix "s-"so it is clear, for example the subset of the full analysis set will be labelled s-FAS etc.
10.4 Efficacy Analysis	The study is non-comparative and non-randomised, the impact of confounding on the measures of performance may be expected and will be evaluated through descriptive analysis of selected baseline and demographic variables and fitting of appropriate models on selected outcomes presented separately for each specialty.	The study is non-comparative and non-randomised, the impact of confounding on the measures of performance may be expected and will be evaluated through descriptive analysis of selected baseline and demographic variables and fitting of appropriate models on selected outcomes presented separately for each specialty. The primary analysis of the following endpoints will be done using FAS and PP analysis population. However, an additional analysis will also be carried out on a subset of these populations (s-FAS and s-PP) which includes only subjects who were recruited post-interim

		analysis and followed protocol version 8.0.
10.4.1 Analysis of Primary Endpoints	Exudate management assessed by no occurrence of exudate leaks as assessed through a combination of leakage alert data from device [redacted] and/or clinical data on any leakage observed during the dressing wearing period resulting or not, in an unplanned dressing change.	Exudate management assessed by no occurrence of exudate leaks as assessed by reported clinical data on any exudate leakage observed through a dressing or around the borders during the dressing wearing period resulting or not, in an unplanned dressing change.
10.4.1 Analysis of Primary Endpoints	Composite Clinical Success (CCS) defined as a binary variable (1/0) (1 if all three of the following are true and 0 if at least one of the three is false): A. Nominal pressure is in the interval 80mmHg ± 7mmHg B. Dressing wear time is 7 days C. No leakage	Composite Clinical Success (CCS) defined as a binary variable (1/0) (1 if all three of the following are true and 0 if at least one of the three is false): A. Average negative pressure within therapeutic range (-100mmHg to -60mmHg) B. Dressing wear time is 7 days C. No exudate leakage
10.4.2 Analysis of Secondary endpoints	• Range of motion assessment (ROM) for the knee at pre-operative visit, post-operative visit, 7, 14 and 30 days.	• Range of motion assessment (ROM) for the knee at pre-operative visit, post-operative visit, 7, 14 and 30 days. (Phase 1 only)
10.4.2 Analysis of Secondary endpoints		Added: As range of motion is collected for subjects in the knee surgery group only there will be no

		summary of ROM in the s-FAS and s-PP analysis.
10.6 Interim Analyses	An interim analysis will be performed mainly for safety assessment purposes, once the study has recruited 22 subjects in specialty each group who have completed the follow-up period. The study will be paused while the MHRA assesses the results.	As a condition for the MHRA No Objection decision, an interim analysis was required to be performed once the study has recruited 22 subjects in each specialty group who had completed the follow-up period. The study was paused while the MHRA assessed the results. There will be no further interim analysis performed as part of Phase 2 of this study.
11 Sample Size Justification	The sample size is justified based on the proposed three primary outcome variables of nominal pressure of 80mmHg, Dressing wear time in days and exudate management based on incidence of exudate leakage. Each of the three hypotheses will be tested separately for each specialty cohort. For the nominal pressure the sample size is based on analysis to test equivalence of negative pressure delivery against the reference value of 80.2mmHg. Previous data extracted from the PICO 7 system were found to be distributed with a SD=14.8. For purposes of sample size calculation, the a priori assumption is that the [redacted] system will have a similar operating pressure to PICO 7, and therefore similar variability	An interim analysis was made after 44 subjects were recruited (22 from each indication). Based on the root cause analysis of seal loss, the study will continue on Abdominal surgical indications only at this time, whilst further investigative work continues into understanding the cause of seal loss in the orthopaedic surgery group. The 2nd phase of the study (post-interim analysis) will be powered according to previous sample size. However, as no further subjects will be recruited for the orthopaedic surgery group, all 44 subjects recruited will be in the abdominal indication group. This will increase the total number of abdominal incisions to 66 (22 recruited following the protocol v7.0 and 44 following v8.0 of the

in pressure delivery is assumed. The following hypotheses will be tested to establish the equivalence in mean operating pressure of [redacted] system over 7 days compared to the reference value for PICO 7 (80.2 mmHg) with equivalence margin, δ1:
H0: |μ - μ 0 | ≥ δ1
Ha: |μ - μ 0 | < δ1
In the stated hypotheses, μ represents the mean operating pressure of [redacted] system and μ0 represents , the reference value relating to the mean operating pressure of PICO 7 (=80.2mmHg, SD=14.8). The equivalence margin, δ1 = 7 mmHg was chosen as a conservative non-clinically significant difference for operating pressure assuming the difference is actually 0. The hypothesis will be tested, separately for each specialty cohort by a two-sided t-test (TOST) at the alpha level of 0.025 (one-sided). If the null hypothesis is rejected, clinical equivalence in terms of pressure delivery will be confirmed. Based on the data used for sample size estimation, thirty eight (38) subjects are required to achieve 80% power to detect equivalence at the significance level of α = 0.025 (one-sided) within 7mmHg using a two-sided t-test. Drawing from past experience, allowing that 15% protocol). This ensures that the primary endpoint is sufficiently powered for both the primary analysis of the abdominal data for all subjects as well as for a secondary analysis to be done on the data from those recruited according to protocol v8.0 only.

of the subjects may be lost to follow up by the end of the study, a sample size of 44 subjects per specialty are needed to achieve sufficient statistical power for each specialty to be analysed separately, within this study. Based on the above, a total of 88 subjects will be recruited, which will include 44 subjects with each of the following specialties: orthopaedics (closed surgical knee incisions, e.g. after total knee arthroplasty), and abdominal surgery (e.g. closed surgical abdominal incisions of which at least 50% would be colorectal cases).
For the management of exudate, measured by incidence of exudate leakage, the sample size is evaluated for adequacy based on the non-leakage rate recorded by the NWPT system. According to internal data collected within Smith and Nephew surgical study involving Closed Abdominal and Orthopaedic subjects, 85% of the PICO NPWT systems had no exudate leaks. Therefore, assuming that [redacted] NWPT system will manage 85% of exudate effectively or better, demonstrated through no exudate leakage observed, a sample size of 10 subjects for each specialty will be sufficient to exclude a response rate of 65% or less with 80% power by

using a 2-sided 95% confidence interval for
For the dressing wear time (in days) the sample size is based on comparison of the [redacted] system compared to the literature derived value for each specialty separately. The mean dressing wear time derived from literature is 4.6 days and a standard deviation of 2.2539. It is projected that the [redacted] NWPT system will have a mean dressing wear time of 7 days with similar distribution to the literature value.
The following hypotheses will be tested, for each specialty separately, to establish that the dressing wear time of the [redacted] system is strictly not worse (lower) than the literature derived value:
H0: μ - μ 0 ≤ 0
Ha: μ - μ 0 >0
In the stated hypothesis, μ the mean [redacted] pump dressing wear time and μ0 represents the literature derived value (4.6 days). A one sided (one sample) t-test with alpha = 0.025 will be used to evaluate the hypothesis for each specialty. Based on the expected mean dressing wear time of 7 days, literature derived value of 4.6 days, and a standard deviation of 2.25 days, 80% power and 2.5%

significance level, a sample size of 10 subjects per specialty is adequate to perform the above the hypothesis separately for each specialty cohort. Therefore, the planned forty-four subjects per specialty cohort are adequate to conclude that the PICO orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions) separately. With the planned 44 subjects per specialty, a response rate below 70% could be excluded for each specialty individually. [redacted] system is strictly not worse (lower) than the literature derived value for each speciality individually. Further, with the planned 44 subjects per specialty, a dressing wear time below 6.0 days could be excluded for each specialty individually for the [redacted] device, represented by the lower limit of the 95% confidence interval lying above 6.0 days, based on assumptions previously listed; one-sided t-test with 80% power, 2.5% significance level, with a standard deviation of 2.25 days and assumed 7 day wear time of the [redacted] device. No adjustment to the sample size calculations will be made to account for interim report related to safety review. The

	sample size was estimated using nQuery Advisor 4.0 and statistical software SAS Version 9.4.	
12 Adverse Events and Device Deficiencies		Updated definitions per ISO14155:2018 Updated reporting requirements as per EC and MHRA approval letters
15.1 CRO		New section: The sponsor has engaged Contract Research Organization (CRO) to assist in conducting this study. When appropriate, the CRO is referred in study documents as "Sponsor's agent."
15.4 Interim Monitoring Visit		New section: Regular interim monitoring visits will be performed by the Sponsor or qualified person designated by the Sponsor.
15.6 Close-out Visit	Study close-out visits 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	Study close-out visits 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

	regarding records retention and IRB/IEC reporting requirements.	IRB/IEC reporting requirements. When no subjects have been included, a remove close-out visit may be conducted.
22 References		Updated Pellino reference Added Flynn and Helito
22.1 Protocol Amendment 8		Added to Document these changes
22.9 IFU		Updated to new version
22.10	Principal Investigator Obligations (ISO14155:2011)	Principal Investigator Obligations (ISO14155:2020) Text updated to reflect latest version
22.11 ASA Physical Status Classification System	Last Amended: October 15,2014 *(original approval: October 15, 2014)*	Last Amended: December 13, 2020 *(original approval: October 15, 2014)*
	ASA IV Examples: Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis	***ASA IV Examples:*** Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
Tables and Figures		Updated captions for automatic referencing

22.2.5 Approval/Notification

These updates are considered a substantial amendment and will be notified to MHRA and submitted for EC approval. The changes will only be implemented after MHRA/EC approval confirmation.

22.3 Protocol Amendment 7

22.3.1 General Purpose

This amendment has been completed to comply with conditions required by MHRA as part of No Objection clearance.

22.3.2 Rationale

Updates to the protocol have been made to address a number of conditions attached to the No Objection certificate issued by MHRA on 25 January 2019.

22.3.3 Effect on Study Status

Not applicable. This amendment is to be in effect and implemented prior to study enrolment.

22.3.4 Details

Section	Revised Text 23/Jan/2019 Version 6.0	Revised Text 18/Mar/2019 Version 7.0
Throughout	Standardisation of use of the terms "subject" vs "patient".	
1.1 Protocol Signature	I agree to comply with the Investigator's Obligations stipulated in Section 27.1 of the protocol	Corrected the PI Obligations section reference to the actual folder number: I agree to comply with the Investigator's Obligations stipulated in Section 20.9 of the protocol

[redacted]

Synopsis 9.1.1		Window for Day 7 Visit corrected to (±1) day to reconcile with the visit window in main discussion on this visit at Section 9.1.6
Synopsis Study Duration	Twelve months from when the first study site is initiated until last enrolled subject reaches last study assessment	Eighteen months from when the first study site is initiated until last enrolled subject reaches last study assessment. This period includes an estimated 6 month period to prepare a mid-recruitment interim report, submit it and obtain feedback form MHRA
Synopsis Secondary Endpoints		Added to comply with MHRA conditions for approval/No Objection: • Range of motion assessment (ROM) for the knee at pre-operative visit, post-operative visit, 7, 14 and 30 days.
Synopsis Inclusion/Exclusion Criteria		Inclusion:Expanded on definition of suitable abdominal/knee incision (see 7.2 below) Exclusion: Clarified a number of statements as response to frequently asked queries from sites (see 7.3 below for full details) Added an exclusion from Section 7.3 which was missed to be copied in the synopsis section: Subjects where the

		[redacted] area of the device would be placed on a load-bearing anatomical location (i.e. areas vulnerable to pressure damage).
Synopsis Study Schematic		Updated the description of activity to reflect eCRF form names: Demographics/Vital Signs/ Medical History/Hx of Substance Use Updated the activity for operative visit to include I/E criteria check. Deleted the "Subject and/or Clinician Reported Outcomes" activity and expanded it to its individual components (Subject Comfort Level and VAS Pain Score, Acceptability of NPWT system to Subject, Assessment of NPWT application by Clinician and Acceptability of NPWT system to Clinician) to facilitate clarity on which reported outcomes are due at specific visits.
3.3		Added ASA and ROM to list of abbreviations
5.2		Added: Range of motion assessment (ROM) for the knee
7.2		Revised Inclusion Criteria to align with literature review for the interim analysis. The ASA score will allow the risk profile to match for the [redacted] study population and the articles that [redacted]

[redacted]

	6. Subject has one suitable closed abdominal or knee surgery incision, (if there is more than one incision then the clinician should choose the one which in their opinion is most suited to PICO therapy) that fits under the absorbent dressing area of the appropriate [redacted] dressing sizes (dressing sizes equivalent to PICO dressings [redacted]	[redacted] results will be compared against, to comply with MHRA conditions for approval/No Objection. 6. In Orthopaedic surgery: subject is scheduled for an elective primary knee replacement arthroplasty and ASA* score of 2-3 7. In Abdominal surgery: subject is scheduled for an elective open gastrointestinal surgery and ASA* score of 2-3 8. Immediately after the surgery, subject will have one suitable closed abdominal or knee surgery incision, (if there is more than one incision, then the clinicians should choose the one which in their opinion is most suited to PICO therapy) that fits under the absorbent dressing area of the appropriate [redacted] dressing sizes (dressing sizes equivalent to PICO dressings [redacted]
7.3		Revised Exclusion Criteria to align with literature review for the interim analysis. The BMI score will allow the risk profile to match for the [redacted] study population and the articles that [redacted] results will be

	3.Participation in the treatment period of another clinical trial within thirty (30) days of operative visit or during the study. 9. Subjects with infected incisions at the time of surgery (except for those with perforated bowel or peritonitis).	compared against, to comply with MHRA conditions for approval/No Objection. The rest of the changes were added to provide clarification to frequently asked questions from potential sites received during pre-selection phase. 3.Participation in the treatment period of another similar clinical trial (wound care related) within thirty (30) days of operative visit or during the study. 9. Subjects with infected skin lesions or incisions at the time of surgery (any area of the body). Added 2 new exclusions: 12.Subjects with a BMI ≥ 40. 13. Subjects undergoing exclusively abdominal laparoscopic surgery (except if the procedure is scheduled to include a laparotomy incision ≥ 5 cm.
8.3.2		Added: • Comparison of Wound and Skin VAS scores at days 7, 14 and 30 as assessed by the treating clinicians versus scores provided by the independent assessor.

[redacted]

		• Range of motion assessment (for knee subjects only) at pre-operative, 1, 7, 14 and 30 days
8.3.3		Added to comply with MHRA conditions for approval/No Objection: A descriptive analysis for clinician's and subject's experience of the device and perception of the device in general will be included in the analysis.
9.1.1		Deleted the "Subject and/or Clinician Reported Outcomes" activity and expanded it to its individual components (Subject Comfort Level and VAS Pain Score, Acceptability of NPWT system to Subject, Assessment of NPWT application by Clinician and Acceptability of NPWT system to Clinician) to facilitate clarity on which reported outcomes are due at specific visits.
9.1.2 9.1.4 9.1.6 9.1.7 9.1.8		Added: Obtain range of motion measurements (for knee subjects only).
9.1.6		Corrected the visit window to +/- 1 day
9.1.9		Streamlined instructions:

		2. Record the complication type. Please provide as much detail as possible.
9.1 9.2	Throughout these sections Updated terminologies to "suitably qualified individual/clinician" instead of "treating investigator" to reflect the differences in site practice.	
9.2.1	Results from secondary endpoint assessments (SSC, SSI rates, etc.) will be compared to published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in similar populations. For the knee patients, secondary endpoints assessment results will be compared to results from complications as described by Karlakki et al [2016][17]. SSC complication rates for colorectal surgery as described by Pellino et al. [2014][24] would be used to compare to results from colorectal patients. For the rest of abdominal surgery patients, we propose to use the rates of complications as described by O'Leary et al [2016][30] As this data	Added text to comply with MHRA condition for approval/No Objection to perform comparative analysis for each endpoint succinctly with published literature pooled from a minimum of 5 research articles. Results from secondary endpoint assessments (SSC, SSI rates, etc.) will be compared to at least five published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in similar populations to comply with the conditions of MHRA Notice of No Objection (Appendix 20.11). To ensure [redacted]population will closely approximate those of the similar research articles that it will be compared against, the Inclusion and Exclusion criteria have been updated. This allows the risk profile of the [redacted] population to be aligned with the review of literature. The additional published papers on

	comparison will be based on secondary endpoints, it will be intended only to explore the potential of [redacted] to safely promote clinical benefits. Relevant published information for this purpose include the following:	similar populations will be identified prior to start inclusion. Data comparison will be part of the interim analysis report, which is planned as described in section 10.6. As this data comparison will be based on secondary endpoints, it will be intended mainly to explore the potential of [redacted] to safely promote clinical benefits. Relevant published information for this purpose include so far the following:
9.2.3		**Assessment of Range of Motion** Range of motion measurements are not routinely measured in PICO studies, and S&N is not expecting [redacted] to impact negatively the knee Range of Motion (ROM). ROM measurements are included as a requirement from MHRA as part of the safety assessment of the device when used over mobile anatomical regions, i.e. joints. Knee ROM will be assessed using a goniometer by a trained member of the study team (e.g. physiotherapist) at each of the specified time points. It is ideal that only one person is assigned this task for the duration of the study. The

<table>
<tr>
<td></td>
<td></td>
<td>assessment will be performed using routine clinical practice to measure flexion and extension of the knee joint. Results from the ROM measurements will be compared to published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in the knee population. Some of the relevant trials are listed below:
<table>
<tr><th>Study (N)</th><th>Flexion at day 1 (in degrees)</th><th>Flexion at day 7</th><th>Study (N)</th></tr>
<tr><td>Hasanai n[36] (78; nA=39 nB=39)</td><td>87.6</td><td>nA=105 ; nB=106 (approx.)</td><td>Hasanai n[36] (78; nA=39 nB=39)</td></tr>
<tr><td>Kayamo ri[37] (67; n1=34, n2=23)</td><td>n1 = 62.3 ± 14.5 ; n2=60.2 ±10</td><td>n1=89.3 ± 8 ; n2=90.1 ± 8.8</td><td>Kayamo ri[37] (67; n1=34, n2=23)</td></tr>
<tr><td>Mutsuza ki[38] (N =26, 39 knees)</td><td>Value at day 1 postop not given</td><td>78.2 ± 15.6</td><td>Mutsuza ki[38] (N =26, 39 knees)</td></tr>
</table>
Where:

nA=patients with tourniquet
nB=patients without tourniquet
n1=patients with compression dressing
n2= patients with standard dressing</td>
</tr>
<tr>
<td>10.4.2</td>
<td></td>
<td>Added:

• Range of motion assessment (ROM) for the knee at pre-operative visit, post-operative visit, 7, 14 and 30 days.</td>
</tr>
</table>

10.6	There is no interim analysis planned for this study as it is not deemed necessary.	An interim analysis will be performed mainly for safety assessment purposes, once the study has recruited 22 subjects in each group who have completed the follow-up period. The study will be paused while the MHRA assesses the results.
11		No adjustment to the sample size calculations will be made to account for interim report related to safety review.
12.2		Minor updates made to align with current safety reporting procedures at S&N.
18	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 12 months.	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 18 months. This includes an estimated six-month pause in enrolment while the interim analysis is reported to the MHRA. The length may be extended by the actual length of interim analysis review.
20.10		Added ASA Physical Status Classification System for reference
20.11		Added MHRA No Objection Letter for reference

22.4 Protocol Amendment 6

22.4.1 General Purpose

This amendment has been completed following further discussion with MHRA.

22.4.2 Rationale

Updates to the protocol have been made to address a number of points raised by the MHRA during their review of the study.

22.4.3 Effect on Study Status

Not applicable. This amendment is to be in effect and implemented prior to subject enrollment.

22.4.4 Details

Section	Revised Text 21/Jan/2019 Version 5.0	Revised Text 23/Jan/2019 Version 6.0
Synopsis	A total of 88 subjects will be recruited to allow for 44 subjects to be recruited from each of the following specialties: orthopaedics (closed knee incisions	A total of 88 subjects will be recruited to allow for 44 subjects to be recruited from each of the following specialties: orthopaedics

	e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions).	(closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions of which at least 50% would be colorectal cases).
9.2.1	Results from secondary endpoint assessments (SSC, SSI rates, etc.) will be compared to published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in similar populations. As this data comparison will be based on secondary endpoints, it will be intended only to explore the potential of [redacted] to safely promote clinical benefits.	Results from secondary endpoint assessments (SSC, SSI rates, etc.) will be compared to published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in similar populations. For the knee patients, secondary endpoints assessment results will be compared to results from complications as described by Karlakki et al [2016][17]. SSC complication rates for colorectal surgery as described by Pellino et al. [2014][24] would be used to compare to results from colorectal patients. For the rest of abdominal surgery patients, we propose to use the rates of complications as described by O'Leary et al [2016][30]. As this data comparison will be based on secondary endpoints, it will be intended only to explore the potential of [redacted] to safely promote clinical benefits.
9.2.1	Keeney el al [2019][35] reported a rate of 12.7% SSC (particularly persistent wound drainage) in a population of orthopaedic patients (n=213] treated with standard dressings after THA and TKA. This included primary and revision surgery as well as patients bearing or not associated surgical risk factors such as BMI >35, diabetes or smoking. In primary TKA (n=126) the	Removed reference to Keeney paper

[redacted]

	rate of SSC was 19%; to notice, in revision TKA patients (n=37) the rate of SSC with standard dressings was 27%. Complications included SSI superficial and deep, persistent wound drainage, and need for revision surgery.	
Table 9.2.1-1		Removed reference to Keeney paper Qualified that Pellini paper is on colorectal patients only
11	Based on the above, a total of 88 patients will be recruited, which will include 44 patients with each of the following specialties: orthopaedics (closed surgical knee incisions, e.g. after total knee arthroplasty), and abdominal surgery (e.g. closed surgical abdominal incisions).	Based on the above, a total of 88 patients will be recruited, which will include 44 patients with each of the following specialties: orthopaedics (closed surgical knee incisions, e.g. after total knee arthroplasty), and abdominal surgery (e.g. closed surgical abdominal incisions of which at least 50% would be colorectal cases).

22.5 Protocol Amendment 5

22.5.1 General Purpose

This amendment has been completed following further discussion with MHRA.

22.5.2 Rationale

Updates to the protocol have been made to address a number of points raised by the MHRA during their review of the study. Changes were made to provide details specialties under the closed surgical wound indication, to add language regarding comparison of the study results with existing evidence/literature for each of the secondary end points, to add details for the secondary end points wound assessment and to provide update to the statistics section.

22.5.3 Effect on Study Status

Not applicable. This amendment is to be in effect and implemented prior to subject enrolment.

22.5.4 Details

Section	**Revised Text 15/Jan/2019** **Version 4.0**	**Revised Text 21/Jan/2019** **Version 5.0**
Synopsis 8.3.2 10.4.2	Added secondary endpoint below: Wound and Skin VAS score assessment at 7, 14 and 30 days.	

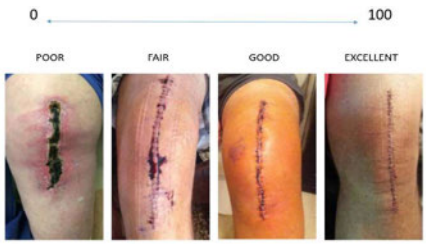
6.1	Appropriate wound types include: • Surgically closed Incision Sites:	Appropriate wound types include: • Surgically closed Incision Sites (Knees and Abdomens)
9.1.3 9.1.6 9.1.7 9.1.8 9.1.9	Assess the surrounding skin (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated).	Assess the surrounding skin including the area under the pump (e.g., healthy, fragile, inflamed, erythema, bruising, eczematous, dry/flaky, macerated).
9.1.6 9.1.7 9.1.8 9.1.9	Photograph the incision using the camera supplied by the Sponsor.	Photograph the incision using the camera [redacted] supplied by the Sponsor. The wound photographs and the resulting wound measures will be stored in a database.
9.1.6 9.1.7 9.1.8 9.1.9		Added new assessment: Record 100mm VAS score for wound and skin assessment

[redacted]

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/epithelialized , ii) an assessment of delayed healing, iii) an assessment of infection, dehiscence or other complications. Incision closure is defined as 100% re-epithelisation without drainage or dressing requirements. Primary or first intention healing occurs when tissue is cleanly incised and re-approximated and healing occurs without complications. The incisional defect re-epithelises rapidly and matrix deposition seals the defect. Incisional wounds are usually completely re-epithelised 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 Closure, SSC and CDC-SSI Incision Assessment** Incision closure is defined as 100% re-epithelisation without drainage or dressing requirements. Primary or first intention healing occurs when tissue is cleanly incised and re-approximated and healing occurs without complications. The incisional defect re-epithelises rapidly and matrix deposition seals the defect. Incisional wounds are usually completely re-epithelised 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 healing and potential complications will be completed by the treating surgeon at each of the specified time points. The assessment will be performed using the CDC definitions of surgical site infection. SSI are infections that occur within 30 days of surgery or within a year if an implant is present. In addition, one of the following criteria must be met: (1) Purulent drainage from an incision (incisional infection) or from a drain below the fascia (deep infection);

	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 leucocytosis 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.	(2) A surgeon or attending physician diagnosing an SSI; (3) An infective organism being isolated from a culture of fluid or tissue obtained from the surgical wound (for incisional infections); (4) Spontaneous dehiscence or a surgeon deliberately re-opening the wound in the presence of fever or local pain, unless subsequent cultures were negative, or an abscess being detected during direct examinations (for deep infections). The grading of SSI is based on symptoms. In case of SSI, there may be also discharge (serous exudate, seropurulent, haemopurulent, pus), delayed healing, erythema, unexpected pain, tenderness, abnormal smell or wound breakdown. 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). Wound dehiscence will also be classified as partial or total. The wound size measurements will be performed directly from the wound photographs taken from the wound per each visit. The camera [redacted] will measure the lengths, the depth

		and the width of the wound automatically, if appropriate. The wound photographs and the resulting wound measures will be stored in a database. Assessment of the wound will also include the use of a validated 100 mm Visual Analogue Scale (VAS) as described by Keeney et al [35], where a very low score is associated to a wound with a major gapping, dehiscence, severe inflammation and/or infection; and a very high score correspond to a completely healed wound with no evidence for inflammation. VAS assessment for wound evolution will be performed by the treating investigator. In addition, 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 a photographic incision assessment. This will include 1) assessment of whether the incision is fully closed/epithelialised, 2) assessment of delayed healing, 3) assessment of infection, dehiscence or other complications. 4) Assessment of any potential AE on the skin under the dressing, and particularly the skin under the pump. 5) Wound assessment using the validated 100 mm VAS

		scoring tool. This assessment will use pictures captured with [redacted]® [redacted] The independent expert will be blinded to time points. Representative images for guidance on the use of the validated 100 mm VAS scale are presented here below.  VAS tool for assessment of closed surgical wounds evolution Results from secondary endpoint assessments (SSC, SSI rates, etc.) will be compared to published data from trials evaluating single use NPWT devices used in the postoperative management of similar closed surgical incisions in similar populations. As this data comparison will be based on secondary endpoints, it will be intended only to explore the potential of [redacted] to safely promote clinical benefits. Relevant published information for this purpose include the following:

		Karlakki et al [2016][17] reported a combined rate of SSC of 8.4% in 107 patients treated with standard dressings (63 hips and 44 knees). If taken separately, the rate of SSC was 13.6% after TKA and 4.7% after THA. Complications included: superficial wound infections, haematoma, and prolonged wound discharge. Keeney el al [2019][35] reported a rate of 12.7% SSC (particularly persistent wound drainage) in a population of orthopaedic patients (n=213] treated with standard dressings after THA and TKA. This included primary and revision surgery as well as patients bearing or not associated surgical risk factors such as BMI >35, diabetes or smoking. In primary TKA (n=126) the rate of SSC was 19%; to notice, in revision TKA patients (n=37) the rate of SSC with standard dressings was 27%. Complications included SSI superficial and deep, persistent wound drainage, and need for revision surgery. Pellino et al. [2014][24] reported in a cohort of 25 colorectal patients, after abdominal surgery, a length of stay of 7.1 days, a rate of seroma of 40%, and a SSI rate of 44% according to CDC criteria. O'Leary et al [2016][30] found a SSI rate of 32% after 30 days

follow up in a cohort of 25 patients, whose closed abdominal incision was treated with standard dressings after undergoing open abdominal surgery. Length of stay for this group was 14.7 days.

A summary of this relevant evidence for the surgical incision proposed in this protocol is presented in Table 9.2.1.1

Reference	**Incision type**	**Reported rate of SSC, (size of cohort) with Standard Dressings**
Karlakki et al [17]	Closed surgical knee incision	13.6% (n=44)
Keeney et al [35]	Closed surgical knee incision	Primary TKA 19% (n=126) Revision TKA 27% (n=37)
Pellino et al [24]	Closed surgical abdominal incision	SSI at 30 days 44% (n=25)
O'Leary et al [30]	Closed surgical abdominal incision	SSI at 30 days 32% (n=25)

Results from this trial will be also compared to actually reported rates of SSC in each one of the research centres (where available) for the concerned specialty and types of surgery.

This assessment will be intended to ensure that [redacted] is not compromising patients'

		safety and importantly will be a clinical comparison, rather than a statistical comparison. The expected results for [redacted] should be to obtain similar or lower complication rates than those associated to standard dressings. A training session will be held for the individuals at each site to standardise how the pictures must be taken and the assessments of complication, infection and dehiscence made.
9.2.2	**Assessment of Surrounding 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.	**Assessment of periwound skin** The skin surrounding the surgical incision will be assessed by the above mentioned clinicians (direct by the treating surgeon and pictorial by the independent expert) to confirm if the skin appears healthy or is fragile, inflamed, eczematous, dry/flaky, macerated or has erythema, bruising. This assessment will also search for any potential adverse events (e.g. skin irritation, allergy, etc.) on the skin under the [redacted] dressing focusing on the skin under the pump. In the case of local wound complications inducing local changes like periwound oedema, skin necrosis, dehiscence, Silhouette pictures will be used

[redacted]

		to assess the evolution of the event until the end of follow-up. [redacted]® [redacted] Wound Assessment Device allows for a precise determination of surface areas, (depth and volume too if required) thus facilitate an objective follow up of the evolution of skin lesions (erythema, dehiscence).
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 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 initials, 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	**Photographs and Surgical Site Assessment** Images of the subject's postsurgical incision (and wound zone) will be captured prior to initial dressing application, at 7 days post operatively (or when dressing is removed), at 14 days and at 30 days postoperatively (or early exit visit) using a digital camera supplied by S&N. Photographic assessment will be performed with the [redacted]® [redacted] [redacted]® [redacted] is a portable device that easily allows capture of high-resolution graphic information about a subject's skin wound, which is then managed, analysed and stored in a central database. Information captured includes photographic images, quantitative measures, and other wound assessment data input by the assessing clinician, all obtained with no subject contact.

	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.	[redacted]® [redacted] builds that information into an electronic record for either printing, electronic uploading to Sponsor's database, further clinical assessment or archiving. Information about performed wound measurements history is available on the system so that progression of the wound status can be calculated and presented. The images will be used to perform wound assessments by the treating investigator, and by an independent expert. Photograph should also be taken where appropriate of all DevD reported. Pictures will also constitute the pictorial record of the study reference incisions. The image should be framed such that the entire incision/dressing area 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 [redacted]® [redacted] camera will be given prior to start of the study. An image of the dressing in place will be taken after application, and before removal, to check the

		device compliance. All photographs should be linked to the relevant assessment on the CRF.
10.4.2		Added paragraph: Where the data is recorded both by the treating investigator, and by an independent medically qualified individual/assessor (for example, the wound and skin VAS score), the assessments will be presented separately for each assessor and results cross-tabulated between assessors where appropriate. In each case analyses will be presented separately for each specialty.
11	The following hypotheses will be tested, for each specialty separately, to establish that the dressing wear time of the [redacted] system is strictly not worse (lower) than the literature derived value: $H_0: \lvert\mu - \mu_0\rvert \geq \delta_1$ $H_a: \lvert\mu - \mu_0\rvert < \delta_1$	The following hypotheses will be tested, for each specialty separately, to establish that the dressing wear time of the [redacted] system is strictly not worse (lower) than the literature derived value: $H_0: \mu - \mu_0 \leq 0$ $H_a: \mu - \mu_0 > 0$
12.1.1 12.1.2. 12.1.3. 12.1.4. 12.1.6	Updated definitions of Adverse Events to align with ISO14155 definitions.	
12.3		Details of medical coding added.

[redacted]

21.2.4	Revised Text 14/Jan/2019 Version 4.0	Revised Text 15/Jan/2019 Version 4.0

22.6 Protocol Amendment 4

22.6.1 General Purpose

This amendment has been completed following discussions with MHRA following the November 2018 resubmission.

22.6.2 Rationale

Updates to the protocol have been made to address a number of points raised by the MHRA during their review of the study. Changes include updates to the specialties included in the study, sample size, number of sites, length of study and stats section.

22.6.3 Effect on Study Status

Not applicable. This amendment is to be in effect and implemented prior to subject enrolment.

22.6.4 Details

Section	Revised Text 6/Nov/2018 Version 3.1	Revised Text 15/Jan/2019 Version 4.0
Throughout	All references to skin graft and split thickness skin grafts were removed.	
Throughout	Standardisation of formatting	
Synopsis	Secondary Objectives: To assess clinical performance and safety of the [redacted] NPWT system within 30 days of surgery through the: • 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] • Percentage of successful skin graft take at Days 7, 14 and 30 • Condition of surrounding skin around the wound bed, and under the pump [redacted] • Any pain experienced by the subject in relation to the [redacted] system	Secondary Objectives: To assess clinical performance and safety of the [redacted] NPWT system within 30 days of surgery through the: • Incidence of Surgical Site Infection (SSI) – Superficial, deep organ space [CDC criteria] • Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep etc.), seroma, necrosis, hematoma, suture abscess] • Condition of skin around the wound, and under the [redacted] • Any pain experienced by the subject in relation to the [redacted] system

Synopsis	Sample Size A total of 44 patients will be recruited to allow a minimum of 10 patients with each of the following indications to be recruited: grafts, closed knee, and closed abdomen. The remainder of the sample will be made up from any of the three permitted indications included in the study. The sample size is adequate to achieve 80% power to detect equivalence to a reference value of 80.2mmHg at the significance level of α = 0.05 with a 7mmHg margin, using a two-sided t-test and allowing for 25% loss to follow-up.	Sample Size A total of 88 subjects will be recruited to allow for 44 subjects to be recruited from each of the following specialties: orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions).
Synopsis	Number of Sites Up to 8.	Number of Sites Up to 6 total (three sites for each of the specialties)
Synopsis	Inclusion and Exclusion Criteria. Deleted skin graft texts from the list of I/E criteria	
Synopsis	Study Duration Five months from when the first study site is initiated until last enrolled subject reaches last study assessment	Study Duration Twelve months from when the first study site is initiated until last enrolled subject reaches last study assessment

Synopsis	Percentage of skin graft take at Days 7, 14 and 30 as assessed by clinician visual assessment	Deleted.
List of Abbreviations	STSG (Split Thickness Skin Graft)	Deleted
4.1	Skin graft as a patient group was removed. Background was updated to include only discussions relevant to orthopaedic and abdominal specialties.	
4.2	Literature Summary was updated to reflect decision to revise the included specialties in this study. Removed skin graft literature discussion. Added discussion for Selvaggi paper: Selvaggi et al[25] published in 2014 the results of a prospective, open-label, controlled study comparing PICO with standard dressing in adults with Crohn's disease undergoing abdominal surgery. Main risk factors were the presence of Crohn's disease, smoking status, corticosteroids and ASA score 2-3. Twenty-five people were treated with PICO and 25 with the standard dressing. Patients were followed for 12 months postoperatively. The primary endpoint was the rate of SSCs. Patients treated with PICO had less SSC rates (OR 0.21, 95%CI 0.15-0.5, p=0.001) resulting in shorter hospital stay. At last follow-up, readmission rates were lower with PICO.	
4.3	All references to skin graft and split thickness skin grafts were removed.	
4.4.1	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	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.

	site, and a reduction of SSI and other SSC.	
5.2	Secondary Objectives updated as per synopsis changes	
5.4	Following recent discussion with the MHRA on the study design, this section have been removed: S&N will follow the requirements of MEDDEV 2.7/1 revision 4 "Clinical Evaluation: A guide for manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC" in order to confirm the clinical safety and clinical performance of [redacted] for CE marking. S&N will follow the requirements of MEDDEV 2.7/1 revision 4 "Clinical Evaluation: A guide for manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC" in order to confirm the clinical safety and clinical performance of [redacted] for CE marking. S&N will use the results of the proposed clinical study on [redacted] in combination with results from extensive published clinical data on PICO Single Use NPWT System for CE marking together with a comprehensive design verification and validation package of evidence for [redacted] As there is a significant amount of clinical evidence to show that PICO (1.5 and 1.6) single use NPWT tethered pump systems may reduce oedema, increase healing and reduce chance of infection, in closed incision/skin grafts and some limited clinical evidence, on skin grafts, and due to the [redacted] system working with the same mechanism of action, this study will aim to show that the Investigational Product (IP) has clinical performance and is safe in the above indications so that users will have confidence to use [redacted] in place of the tethered systems.	

6.1	Appropriate wound types include:
	
	• Surgically closed Incision Sites:
	  • Cardiothoracic
	  • C-section
	  • General surgery (laparotomy)
	  • Orthopaedic
		Appropriate wound types include:
		
		• Surgically closed Incision Sites

[redacted]

	• Split Thickness Skin grafts (STSG)	
7.1	Approximately 44 patients scheduled for abdominal, knee or skin graft surgery will be recruited to the study and will receive [redacted] The patients will be recruited from up to 8 sites in the United Kingdom and EU. Sites failing to enrol may be replaced. There will be a minimum number of 10 recruited per surgical group (abdominal, knee, Skin grafts).	Approximately 88 patients scheduled for abdominal or knee surgery will be recruited to the study and will receive [redacted] The patients will be recruited from up to 6 sites in the United Kingdom and EU. Sites failing to enrol may be replaced. There will 44 patients recruited per surgical group (abdominal, knee) and 3 research sites per surgical specialty.
7.2	6. Subject has one suitable closed abdominal or knee surgery incision, or Split Thickness Skin Graft (STSG) (meshed or non-meshed) (if there is more than one incision or STSG then the clinician should choose the one which in their opinion is most suited to PICO therapy) that fits under the absorbent dressing area of the appropriate [redacted] dressing sizes (dressing sizes equivalent to PICO dressings [redacted]	6. Subject has one suitable closed abdominal or knee surgery incision, (if there is more than one incision then the clinician should choose the one which in their opinion is most suited to PICO therapy) that fits under the absorbent dressing area of the appropriate [redacted] dressing sizes (dressing sizes equivalent to PICO dressings [redacted]
7.3	8. Subjects with incisions or skin grafts that are actively bleeding unless haemostasis has been achieved (to be confirmed during surgery).	8. Subjects with incisions that are actively bleeding unless haemostasis has been achieved (to be confirmed during surgery).
7.3	9. Subjects with infected skin grafts or incisions at the time of	9. Subjects with infected incisions at the time of surgery (except for those with

	surgery (except for those with perforated bowel or peritonitis).	perforated bowel or peritonitis).
7.3	12. Subjects with split thickness skin grafts to correct venous ulcers where compression therapy is needed for healing (based on clinicians expertise).	Removed Exclusion criteria #12
8.1	It is anticipated that up to 9 sites will participate within the UK and EU.	It is anticipated that up to 6 sites will participate within the UK and EU.
8.3.2	Secondary Endpoints • Clinical performance and safety of the [redacted] NPWT system over a 30 day follow-up period to include: • Incidence of Surgical Site Infection (SSI) – Superficial, deep, organ [CDC criteria] within 30 days of surgery • Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep/organ.), seroma, necrosis, hematoma, suture abscess] within 30 days of surgery • Percentage of skin graft take at Days 7, 14 and 30 as assessed by clinician visual assessment • Condition of peri-wound skin and skin under the [redacted] assessed through visual inspection at 7, 14 and 30 days. • Level of pain during wear of the [redacted] system, and at dressing removal assessed by VAS scale following 7 day therapy	Secondary Endpoints Clinical performance and safety of the [redacted] NPWT system over a 30 day follow-up period to include: • Incidence of Surgical Site Infection (SSI) – Superficial, deep, organ [CDC criteria] within 30 days of surgery. • Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep, partial/total), seroma, necrosis, hematoma, suture abscess] within 30 days of surgery • Condition of peri-wound skin and skin under the [redacted] assessed through visual inspection at 7, 14 and 30 days. • Level of pain during wear of the [redacted] system, and at dressing removal assessed by VAS scale following 7 day therapy

8.4.3	The study includes a single indication in three different surgical specialties and a range of contoured areas of the body where it may be difficult to obtain an effective negative pressure seal and where there may be a range of motion throughout therapy (i.e knee).	The study includes a single indication in two different surgical specialties and a range of contoured areas of the body where it may be difficult to obtain an effective negative pressure seal and where there may be a range of motion throughout therapy (i.e. knee).
9.1.1		Removed skin graft and skin graft complications assessments in schedule of assessments table
9.1.3	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), STSG (meshed / unmeshed) and reference wound type)].	2. Commence operation and collect surgery data [e.g. Type of surgery (closed surgical incision, (type of abdominal surgery, type of knee surgery, incision length, anatomical location and method of closure)].
9.1.3	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))	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), surgical bioburden level (clean/clean-contaminated/ contaminated/dirty), intraoperative warming (yes/no))

9.1.3	5. Photograph incision/skin graft using the camera provided by the Sponsor.	5. Photograph incision using the camera provided by the Sponsor.
9.1.3	6. Assess the incision/skin graft characteristics for likelihood of SSC (oedema, seroma, haematoma, skin necrosis, graft loss).	6. Assess the incision characteristics for likelihood of SSC (oedema, seroma, haematoma, skin necrosis).
9.1.6, 9.1.7 9.1.8 9.1.10.2 9.2.1. 9.2.2 9.2.3	Deleted references to skin graft	
9.1.9	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).	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, partial dehiscence, total dehiscence).
10.1		New text: All summaries and analyses will be presented separately for each of the two cohorts of specialties recruited within the study: orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions). No data will be combined between the two specialties.
10.1	Primary, secondary, and exploratory outcome variables and derived variables will also be summarised accordingly.	Primary, secondary, and exploratory outcome variables and derived variables will also be summarised accordingly separately by specialty.
10.2	Statistical analysis will be performed using each of the patient populations as follows. Analysis of the primary, secondary and exploratory performance objectives will be performed separately using both the Full Analysis Set and the Per Protocol Population. All safety analyses will utilize the Safety Population.	Statistical analysis will be performed using each of the patient populations as follows. Analysis of the primary, secondary and exploratory performance objectives will be performed separately using both the Full Analysis Set and the Per Protocol Population, for each specialty. All safety analyses will utilize the Safety Population, separately for each specialty.
10.4	The study is non-comparative and non-randomised, the impact of confounding on the measures of performance may be expected and will be evaluated through descriptive analysis of selected baseline and demographic variables and	The study is non-comparative and non-randomised, the impact of confounding on the measures of performance may be expected and will be evaluated through descriptive analysis of selected baseline and demographic variables and fitting of appropriate models

	fitting of appropriate models on selected outcomes	on selected outcomes, presented separately for each specialty.
10.4.1	The following hypotheses will be tested to establish equivalence of the [redacted] compared to the internally derived value, with equivalence margin, $\delta_1>0$: $H_0: \lvert\mu - \mu_0\rvert \geq \delta_1$ $H_a: \lvert\mu - \mu_0\rvert < \delta_1$	The following hypotheses will be tested to establish equivalence of the [redacted] system compared to the internally derived value, with equivalence margin, $\delta_1>0$, for each specialty cohort: $H_0: \lvert\mu - \mu_0\rvert \geq \delta_1$ $H_a: \lvert\mu - \mu_0\rvert < \delta_1$
10.4.1	In the stated hypotheses, μ represents the assumed mean operating pressure (80.2 mmHg) and $\mu 0$ represents the mean [redacted] pump operating pressure. The equivalence limit ·1 = 7mmHg was chosen as a conservative non-clinically significant difference assuming that the difference is actually 0. The hypothesis will be tested by two-one-sided t-test (TOST) at the alpha level of 0.05. If the null hypothesis is rejected, equivalence will be confirmed. A two-one sided t-test and corresponding CI will be used to evaluate this hypothesis. • Dressing wear time in days as assessed through a combination of; data from device [redacted] and CRF	In the stated hypotheses, μ represents the assumed mean operating pressure (80.2 mmHg) and μ_0 represents the mean [redacted] pump operating pressure. The equivalence limit δ_1 = 7mmHg was chosen as a conservative non-clinically significant difference assuming that the difference is actually 0. The hypothesis will be tested by two-one-sided t-test (TOST) at the alpha level of 0.025 (one-sided), separately for each specialty. If the null hypothesis is rejected, equivalence will be confirmed. The corresponding 95% CI for each cohort will also be presented.. • Dressing wear time in days as assessed through a combination of; data from device [redacted] and CRF

	recorded data of any unplanned dressing change. The following hypotheses will be tested to establish equivalence of the [redacted] system compared to the literature derived value, with equivalence margin, ·1>0: H0: |μ - μ 0 | ≥ ·1 Ha: |μ - μ 0 | < ·1 In the stated hypothesis, μ represents the assumed mean dressing wear time in days and μ0 represents the mean [redacted] pump dressing wear time. The equivalence margin is 2.4 days. A two-one sided t-test with alpha = 0.05 will be used to evaluate the hypothesis. A binary variable accounting for below 7 days wear off time will also be used and the proportion wearing of before 7 days will be reported as a percentage along with corresponding confidence interval. If necessary and if data allows, important associated factors will be adjusted for in a logistic model. • Exudate management assessed by no occurrence of exudate leaks as assessed through a combination of leakage alert data from device	recorded data of any unplanned dressing change. The following hypotheses will be tested, for each specialty separately, to establish that the dressing wear time of the [redacted] system is strictly no worse (lower) than the literature derived value: $H_0: \mu - \mu_0 \leq 0$ $H_a: \mu - \mu_0 > 0$ In the stated hypothesis, μ represents the mean [redacted] dressing wear time in days and μ0 represents the literature derived value (4.6 days). A one sided (one sample) t-test with alpha = 0.025 will be used to evaluate the hypothesis for each specialty, the corresponding 95% CIs will also be presented. A binary variable indicating <7 / ≥7 days wear time (denoted by 0/1) will also be used and the proportion of dressings with a wear time ≥7 days will be reported as a percentage along with corresponding 95% confidence interval, for each specialty cohort. If necessary and if data allows, important associated factors will be

	[redacted] and/or clinical data on any leakage observed during the dressing wearing period resulting or not, in an unplanned dressing change. A binary variable for the non-leakage and leakage will be used and the proportion of reported/identified leaks will be presented as a frequency together with a percentage and a 95% CI. The non-leakage proportion for the study will be tested using the Exact test to establish if it is different from the literature derived value of 85% projected. The lower limit of 95% CI will be evaluated to establish if it excludes values of 65% and below. The logistic model will be used to evaluate the adjusted and the un-adjusted models for the CCS primary outcome variable. The variables considered important and to be included in the final model are Age, Diabetic status and the presence of any other comorbidity as a binary variable. All other baseline and medical factors collected at baseline will be evaluated for importance in adjusted models and only those statistically significant in an un-adjusted model will be considered in the final model.	adjusted for in a logistic model. • Exudate management assessed by no occurrence of exudate leaks as assessed through a combination of leakage alert data from device [redacted] and/or clinical data on any leakage observed during the dressing wearing period resulting or not, in an unplanned dressing change. A binary variable for the non-leakage and leakage will be used and the proportion of reported/identified leaks will be presented as a frequency together with a percentage and a 95% CI separately for each specialty. For each specialty, the non-leakage proportion for the study will be tested using the Exact test to establish if it is different from the literature derived value of 85% projected. Further, the resulting lower limit of 95% CI for each specialty will be evaluated to establish if it excludes values of 65% and below. Composite Clinical Success (CCS) defined as a binary variable (1/0) (1 if all three of the following are true and 0 if

	Composite Clinical Success (CCS) defined as a binary variable (1/0) (1 if all three of the following are true and 0 if at least one of the three is false): A. Nominal pressure is in the interval 80mmHg ± 7mmHg B. Dressing wear time is 7 days C. No leakage The Composite Clinical Success (CCS) will be reported as a count and percentage with a 95% CI.	at least one of the three is false): A.Nominal pressure is in the interval 80mmHg ± 7mmHg B.Dressing wear time is 7 days C.No leakage The Composite Clinical Success (CCS) will be reported as a count and percentage with a 95% CI separately for each specialty. A logistic model will be used to evaluate the adjusted and the un-adjusted models for the CCS primary outcome variable for each specialty, separately. The variables considered important and to be included in the final model are Age, Diabetic status and the presence of any other co-morbidity as a binary variable. All other baseline and medical factors collected at baseline will be evaluated for importance in adjusted models and only those statistically significant in an un-adjusted model will be considered in the final model.
10.4.2	• Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep/organ.), seroma, necrosis, hematoma, suture abscess] within 30 days of surgery	• Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep partial/total), seroma, necrosis, hematoma, suture

		abscess] within 30 days of surgery
10.4.2	• Percentage of skin graft take at Days 7, 14 and 30 as assessed by clinician visual assessment	Deleted
10.4.2	Language added to show that reporting of endpoints will be done separately for each specialty	
11	The sample size is justified based on the proposed three primary outcome variables of nominal pressure of 80mmHg, Dressing wear time in days and exudate management based on incidence of exudate leakage. For the nominal pressure the sample size is based on analysis to test equivalence of negative pressure delivery against the reference value of 80.2mmHg. Previous data extracted from the PICO 7 system was found to be distributed with a SD=14.8. For purposes of sample size calculation, the apriori assumption is that the [redacted] system will have a similar operating pressure to PICO 7, and therefore similar variability in pressure delivery is assumed. The following hypotheses will be tested to establish the clinical equivalence in mean operating pressure of [redacted] system over 7 days compared to the	The sample size is justified based on the proposed three primary outcome variables of nominal pressure of 80mmHg, Dressing wear time in days and exudate management based on incidence of exudate leakage. Each of the three hypotheses will be tested separately for each specialty cohort. For the nominal pressure the sample size is based on analysis to test equivalence of negative pressure delivery against the reference value of 80.2mmHg. Previous data extracted from the PICO 7 system were found to be distributed with a SD=14.8. For purposes of sample size calculation, the a priori assumption is that the [redacted] system will have a similar operating pressure to PICO 7, and therefore similar variability in pressure delivery is assumed. The following hypotheses will be tested to

	reference value for PICO 7 (80.2 mmHg) with equivalence margin, ·1: H0: |μ - μ 0 | ≥ ·1 Ha: |μ - μ 0 | < ·1 In the stated hypotheses, μ represents the mean operating pressure of [redacted] system and μ 0 represents , the reference value relating to the mean operating pressure of PICO 7 (=80.2mmHg, SD=14.8). The equivalence margin, ·1 = 7 mmHg 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-sided t-test at the alpha level of 0.05. If the null hypothesis is rejected, clinical equivalence in terms of pressure delivery will be confirmed. Based on the data used for sample size estimation, thirty eight (38) subjects are required to achieve 80% power to detect equivalence at the significance level of α = 0.025 within 7mmHg using a two-sided t-test. Drawing from past experience, allowing that 15% of the subjects may be lost to follow up by the end of the study, a sample size of	establish the equivalence in mean operating pressure of [redacted] system over 7 days compared to the reference value for PICO 7 (80.2 mmHg) with equivalence margin, δ1: H0: |μ - μ 0 | ≥ δ1 Ha: |μ - μ 0 | < δ1 In the stated hypotheses, μ represents the mean operating pressure of [redacted] system and μ_0 represents , the reference value relating to the mean operating pressure of PICO 7 (=80.2mmHg, SD=14.8). The equivalence margin, δ1 = 7 mmHg was chosen as a conservative non-clinically significant difference for operating pressure assuming the difference is actually 0. The hypothesis will be tested, separately for each specialty cohort by a two-sided t-test (TOST) at the alpha level of 0.025 (one-sided). If the null hypothesis is rejected, clinical equivalence in terms of pressure delivery will be confirmed. Based on the data used for sample size estimation, thirty eight (38) subjects are required to achieve 80% power to detect equivalence at the significance level of α =

	approximately 44 subjects are needed in this study. A total of 44 patients will be recruited to allow a minimum of 10 patients with each of the following indications to be recruited: grafts, closed knee, and closed abdomen. The remainder of the sample will be made up from any of the three permitted indications included in the study. For the management of exudate, measured by incidence of exudate leakage, the sample size is evaluated for adequacy based on the non-leakage rate recorded by the NWPT system. According to internal data collected within Smith and Nephew surgical study involving Cardiothoracic, Cardiovascular and Orthopaedic subjects, 85% of the PICO NPWT systems had no exudate leaks. Therefore, assuming that [redacted] NWPT system will manage 85% of exudate effectively or better, demonstrated through no exudate leakage observed, a sample size of 30 subjects will be sufficient to exclude a response rate of 65% or less with 80% power by using a 2-sided 95% confidence interval. With the full 44 subjects a response rate below 70% could be	0.025 (one-sided) within 7mmHg using a two-sided t-test. Drawing from past experience, allowing that 15% of the subjects may be lost to follow up by the end of the study, a sample size of 44 subjects per specialty are needed to achieve sufficient statistical power for each specialty to be analysed separately, within this study. Based on the above, a total of 88 patients will be recruited, which will include 44 patients with each of the following specialties: orthopaedics (closed surgical knee incisions, e.g. after total knee arthroplasty), and abdominal surgery (e.g. closed surgical abdominal incisions). For the management of exudate, measured by incidence of exudate leakage, the sample size is evaluated for adequacy based on the non-leakage rate recorded by the NWPT system. According to internal data collected within Smith and Nephew surgical study involving Closed Abdominal and Orthopaedic subjects, 85% of the PICO NPWT systems had no exudate leaks. Therefore, assuming that [redacted] NWPT system will manage 85% of exudate effectively or better, demonstrated through no

	excluded. For the dressing wear time the sample size is based on non-inferiority of the [redacted] system compared to the literature derived value. The mean dressing wear time derived from literature is 4.6 days and a standard deviation of 2.2539. It is projected that the [redacted] NWPT system will have a mean dressing wear time of 7 days, therefore assuming a non-inferiority limit of 2.4 days is logical, assuming the acceptable value will lie above 4.6 days. The following hypotheses will be tested to establish non-inferiority of the [redacted] system compared to the literature derived value, non-inferiority margin, $\cdot_1>0$: $H_0: \lvert\mu - \mu_0\rvert \geq \cdot_1$ $H_a: \lvert\mu - \mu_0\rvert < \cdot_1$ In the stated hypothesis, μ represents the assumed mean dressing wear time in days and μ0 represents the mean [redacted] pump dressing wear time. The non-inferiority margin is 2.4 days. A two-one sided sample t-test with alpha =	exudate leakage observed, a sample size of 30 subjects for each specialty will be sufficient to exclude a response rate of 65% or less with 80% power by using a 2-sided 95% confidence interval for orthopaedics (closed knee incisions e.g. after Total Knee Arthroplasty), and Abdominal surgery (closed abdominal surgical incisions) separately. With the planned 44 subjects per specialty, a response rate below 70% could be excluded for each specialty individually. For the dressing wear time (in days) the sample size is based on comparison of the [redacted] system compared to the literature derived value for each specialty separately. The mean dressing wear time derived from literature is 4.6 days and a standard deviation of 2.2539. It is projected that the [redacted] NWPT system will have a mean dressing wear time of 7 days with similar distribution to the literature value. The following hypotheses will be tested, for each specialty separately, to establish that the dressing wear time of the [redacted] system is strictly not

	0.025 will be used to evaluate the hypothesis. Based on the mean dressing wear time of 7 days and a standard deviation of 2.25, an noninferiority margin of 2.4 days, 80% power and 5% significance level, a sample size of 33 subjects is adequate to test for non-inferiority. Therefore, forty-four subjects are adequate to conclude noninferiority. The sample size was estimated using nQuery Advisor 4.0 and statistical software SAS Version 9.4.	worse (lower) than the literature derived value: H_0: $\lvert\mu - \mu_0\rvert \geq \delta_1$ H_a: $\lvert\mu - \mu_0\rvert < \delta_1$ In the stated hypothesis, μ the mean [redacted] pump dressing wear time and μ0 represents the literature derived value (4.6 days). A one sided (one sample) t-test with alpha = 0.025 will be used to evaluate the hypothesis for each specialty. Based on the expected mean dressing wear time of 7 days, literature derived value of 4.6 days, and a standard deviation of 2.25 days, 80% power and 2.5% significance level, a sample size of 33 subjects per specialty is adequate to perform the above hypothesis separately for each specialty cohort. Therefore, the planned forty-four subjects per specialty cohort are adequate to conclude that the [redacted] system is strictly not worse (lower) than the literature derived value for each speciality individually. Further, with the planned 44 subjects per specialty, a dressing wear time below 6.0 days could be excluded for each specialty individually for the [redacted] device, represented by the lower limit of the 95% confidence interval lying above

		6.0 days, based on assumptions previously listed; one-sided t-test with 80% power, 2.5% significance level, with a standard deviation of 2.25 days and assumed 7 day wear time of the [redacted] device. The sample size was estimated using nQuery Advisor 4.0 and statistical software SAS Version 9.4.
18	Following recent discussion with the MHRA on the study design, the following texts have been removed: 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 CE marking of the IP. S&N will follow the requirements of MEDDEV 2.7/1 revision 4 "Clinical Evaluation: A guide for manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC" in order to confirm the clinical safety and clinical performance of [redacted] for CE marking. S&N will use the results of the proposed clinical study on [redacted] in combination with results from extensive published clinical data on PICO Single Use NPWT System for CE marking together with a comprehensive design verification and validation package of evidence for [redacted]	

22.7 Protocol Amendment 3

22.7.1 General Purpose

This amendment has been completed following MHRA objection to the study and suggested amendments to the protocol and to align with our commitment to the MHRA that we will use Meddev Rev 4 CER process for CE marking purposes.

22.7.2 Rationale

Updates to the protocol have been made to address a number of points raised by the MHRA during their review of the study. Namely updates to the statistical section and removal of reference to efficacy throughout the document.

22.7.3 Details

Section	Current Text 26/Jun/2018 Version 2.0	Revised Text 10/Oct/2018 Version 3.0
Study Title	[redacted] Pre-Registration Study: Prospective, Multicentre Trial to assess performance, safety and efficacy of [redacted]	[redacted] Pre-Registration Study: Prospective, Multicentre Trial to assess performance and safety of [redacted]
Throughout	Reference to efficacy removed: 2.0 Study purpose 2.0 Secondary objectives 2.0 Secondary endpoints 5.4 Claims	
Throughout	Reference to efficacy replaced with clinical performance: 4.3 Study Purpose, Para 1, sentences 4, 5 and 7. 5.2 Secondary objectives 8.1 Study Design Para 1 8.3.2 Secondary Endpoints. Bullet 1. 10.4.2 Analysis of secondary endpoints. Para 1.	
	Standardisation of formatting	
2.0	Forty four (44) subjects will be recruited to allow for 10 patients for each of the four selected indications of grafts, closed knee, closed abdomen and unspecified and allow for attrition. The sample size is adequate to achieve 80% power to detect equivalence to a	Forty four (132) subjects will be recruited to allow a minimum of 38 subjects with each of the following indications to be recruited: grafts, closed knee, and closed abdomen. The remainder of the sample will be made up from any of the three

Section	Current Text 26/Jun/2018 Version 2.0	Revised Text 10/Oct/2018 Version 3.0
	reference value of 80.2mmHg at the significance level of α = 0.05 with a 7mmHg margin, using a two-sided t-test and allowing for 25% loss to follow-up.	permitted indications included in the study. The sample size is adequate to achieve 80% power to detect equivalence to a reference value of 80.2mmHg at the significance level of α = 0.05 with a 7mmHg margin, using a two-sided t-test and allowing for 15% loss to follow-up.
3.3		List of Abbreviations updated
5.4	The study is being performed so that performance, safety and clinical efficacy can be confirmed for the [redacted] product for CE marking. There is a need to generate clinical evidence for the [redacted] NPWT system to demonstrate performance, safety and efficacy of the device prior to CE mark as this is a sufficiently distinct technology from current tethered PICO single use NPWT systems. As there is a significant amount of clinical evidence to show that PICO (1.5 and 1.6) single use NPWT tethered pump systems may reduce oedema, increase healing and reduce chance of infection, in closed incision/skin grafts and some limited clinical evidence, on skin grafts, and due to the [redacted] system working with the same mechanism of action, this study will aim to show that the Investigational Product (IP) has clinical efficacy and is safe in the	The study is being performed so that safety and clinical performance can be confirmed for the [redacted] product. S&N will follow the requirements of MEDDEV 2.7/1 revision 4 "Clinical Evaluation: A guide for manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC" in order to confirm the clinical safety and clinical performance of [redacted] for CE marking. S&N will use the results of the proposed clinical study on [redacted] in combination with results from extensive published clinical data on PICO Single Use NPWT System for CE marking together with a comprehensive design verification and validation package of evidence for [redacted] As there is a significant amount of clinical evidence to show that PICO (1.5 and 1.6) single use NPWT

Section	Current Text 26/Jun/2018 Version 2.0	Revised Text 10/Oct/2018 Version 3.0
	above indications so that users will have confidence to use [redacted] in place of the tethered systems.	tethered pump systems may reduce oedema, increase healing and reduce chance of infection, in closed incision/skin grafts and some limited clinical evidence, on skin grafts, and due to the [redacted] system working with the same mechanism of action, this study will aim to show that the Investigational Product (IP) has clinical performance and is safe in the above indications so that users will have confidence to use [redacted] in place of the tethered systems.
10.2	Analysis of the primary, secondary and exploratory efficacy objectives will be performed separately using both the Full Analysis Set and the Per Protocol Population.	Analysis of the primary, secondary and exploratory performance objectives will be performed separately using both the Full Analysis Set and the Per Protocol Population.
10.4	Heading changed: EFFICACY ANALYSIS	Heading Changed: OUTCOME ANALYSIS
10.4.1	First sub-heading changed: Pressure maintenance at nominal 80mmHg	First sub-heading changed: Negative Pressure maintenance at nominal 80mmHg
10.4.1	The following hypothesis will be tested to establish the non-inferiority of the [redacted] system exudate management to the literature derived value of 85% with non-inferiority margin, $\delta_1>0$: $H_0: \pi - \pi_0 \geq \delta_1$	Text deleted

Section	Current Text 26/Jun/2018 Version 2.0	Revised Text 10/Oct/2018 Version 3.0
	H_a: $\pi - \pi_0 < \delta_1$ In the stated hypothesis, π represents the assumed proportion of exudate managed through evaporation and π_0 represents the mean [redacted] pump proportion of exudate managed through evaporation. The non-inferiority margin is 10%. An Exact test for non-inferiority of the study proportion to the literature derived 85% assuming a non-inferiority limit of -10%. A binary variable also for the leakage will also be used and the proportion of reported/identified leaks will be presented as a frequency together with a percentage and a 95% CI.	
10.4.2 Para	Clinical efficacy and safety of the [redacted] NPWT system over a 30 day follow-up period to include:	Clinical performance and safety of the [redacted] NPWT system over a 30 day follow-up period to include:
11 Para 1	The sample size is justified based on the proposed three primary outcome variables of nominal pressure of 80mmHg, Dressing wear time of 7 days and exudate managed through evaporation, 85%. .	
	For the exudate managed through evaporation the sample size is based on non-inferiority test. The expected exudate managed through evaporation is 74-85% (high to low exuding wounds)[34,39]. We expect the [redacted]	For the management of exudate, measured by incidence of exudate leakage, the sample size is evaluated for adequacy based on the non-leakage rate recorded by the NWPT system. According to internal data

Section	Current Text 26/Jun/2018 Version 2.0	Revised Text 10/Oct/2018 Version 3.0
	NWPT system to manage at least 74 - 85% of exudate through evaporation in high to low exuding wounds or better. A non-inferiority margin of -10% is reasonable under the assumptions. The following hypothesis will be tested to establish the no-inferiority of the [redacted] system exudate managed through evaporation to the literature derived value of 85% with non-inferiority margin, $\delta_1>0$: $H_0: \pi - \pi_0 \geq \delta_1 H_a: \pi - \pi_0 < \delta_1$ In the stated hypothesis, π represents the assumed proportion of exudate managed through evaporation and π0 represents the mean [redacted] pump proportion of exudate managed through evaporation. Therefore assuming that [redacted] NWPT system will manage 85% of exudate through evaporation or better, a non-inferiority limit of -10%, a null proportion of 85%, and 5% significance level. A sample of 30 subjects is adequate to test for non-inferiority with 90% power with a lower critical sample value of 25 subjects. Therefore, forty-four subjects are adequate to conclude non-inferiority.	collected within Smith and Nephew surgical study involving Cardiothoracic, Cardiovascular and Orthopaedic subjects, 85% of the PICO NPWT systems had no exudate leaks. Therefore, assuming that [redacted] NWPT system will manage 85% of exudate effectively or better, demonstrated through no exudate leakage observed, a sample size of 30 subjects will be sufficient to exclude a response rate of 65% or less with 80% power by using a 2-sided 95% confidence interval. With the full 44 subjects a response rate below 70% could be excluded.
18 Para 2		Additional Text: S&N will follow the requirements of MEDDEV 2.7/1 revision 4 "Clinical Evaluation: A guide for

Section	Current Text 26/Jun/2018 Version 2.0	Revised Text 10/Oct/2018 Version 3.0
		manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC" in order to confirm the clinical safety and clinical performance of [redacted] for CE marking. S&N will use the results of the proposed clinical study on [redacted] in combination with results from extensive published clinical data on PICO Single Use NPWT System for CE marking together with a comprehensive design verification and validation package of evidence for [redacted]

22.7.4 Additional Modifications

The following modifications are required to correct some aspects of amendment 3 (synopsis not updated in line with change to sample size and error in table header). In addition an error in eligibility criteria no 12 has been corrected.

This amendment is to be in effect and implemented prior to any subject enrolment.

Section	Current Text 10/Oct/2018 Version 3.0	Revised Text 06/Nov/2018 Version 3.1
Study Synopsis: sample size	Forty four (44) subjects will be recruited to allow for 10 patients for each of the four selected indications of grafts, closed knee,	A total of 44 patients will be recruited to allow a minimum of 10 patients with each of the following indications to be recruited: grafts, closed knee,

Section	Current Text 10/Oct/2018 Version 3.0	Revised Text 06/Nov/2018 Version 3.1
	closed abdomen and unspecified and allow for attrition.	and closed abdomen. The remainder of the sample will be made up from any of the three permitted indications included in the study.
7.3, item 12.	Subjects with split thickness skin grafts to correct pressure ulcers where compression therapy is needed for healing (based on clinicians expertise).	Subjects with split thickness skin grafts to correct venous ulcers where compression therapy is needed for healing (based on clinicians expertise).
21.1.4	Error in table header regarding date of revised text has been corrected from 26Sep2018 to 10Oct 2018	

22.8 Protocol Amendment 2

22.8.1 General Purpose

This amendment was completed following initial MHRA review of the protocol.

22.8.2 Rationale

Updates to the protocol were made to address a number of points raised by the MHRA during their review of the study. Namely updates and corrections to referencing throughout, an increase to the length of time for any potential participants since surgery at the same anatomical site, a decrease in the number of sites due to concerns of heterogenecity, additional information added to the statistical section.

22.8.3 Effect on Study Status

Not applicable; this amendment is to be in effect and implemented prior to subject enrollment.

22.8.4 Details

This amendment specifically revised the protocol as follows:

Throughout Updates made to correct referencing

Sample size increased from 40 to 44

Introduction Section 4.1.1

The following text has been added

"However, this may be linked to a high-risk population. Indications for surgery were multiple (cancer (86%), trauma and chronic wounds), in patients relatively old and having multiple

comorbidities. From all the factors assessed, only three showed statistical significance, BMI >30, peripheral vascular disease (PVD) and the concomitant use of immuno-suppressants. On the contrary, in burn patients, who have a good tissue vascularity, the rate of skin graft success when using NPWT has been reported to be higher than 90%"

and later in the same section:

"Although this figure encompasses all causes of readmissions it has been suggested that wound complications (including superficial infections, superficial dehiscence, and delayed healing) following total hip and knee arthroplasty may contribute heavily.

Subject Population Section 7.1

The text "The patients will be recruited from up to 16 sites in the United Kingdom and EU." has been changed to, "The patients will be recruited from up to 8 sites in the United Kingdom and EU."

Exclusion criteria Section 7.3

The text "Patients attending for an operation at the same surgery site (anatomical location) within the last 1 month." has been changed to, "Patients attending for an operation at the same surgery site (anatomical location) within the last 3 months."

Statistical Section 10.4.1

Old text:

- Pressure maintenance at nominal 80mmHg

The following hypotheses will be tested to establish equivalence of the [redacted] system compared to the internally derived value, with equivalence margin, $\delta_1 > 0$:

$H_0: \pi - \pi_0 \geq \delta_1$
$H_a: \pi - \pi_0 < \delta_1$

In the stated hypotheses, μ represents the assumed mean operating pressure (80.2 mmHg) and μ_o represents the mean [redacted] pump operating pressure. The equivalence limit δ_1 = 7mmHg was chosen as a conservative non-clinically significant difference assuming that the difference is actually 0. The hypothesis will be tested by two-sided t-test at the alpha level of 0.05. If the null hypothesis is rejected, equivalence will be confirmed.

A one sample t-test and corresponding CI will be used to evaluate this hypothesis.

- Dressing wear time (7 days) as assessed through a combination of; data from device [redacted] and CRF recorded data of any unplanned dressing change.

The mean dressing wear time will be reported together with the standard deviation. A binary variable accounting for below 7 days wear off time will also be used and the proportion wearing of before 7 days will be reported as a percentage along with corresponding confidence interval. If necessary and if data allows, important associated factors will be adjusted for in a logistic model.

- Exudate management assessed by no occurrence of exudate leaks as assessed through a combination of leakage alert data from device [redacted] and/or clinical data on any leakage observed during the dressing wearing period resulting or not, in an unplanned dressing change

A binary variable also for the leakage will also be used and the proportion of reported/identified leaks will be presented as a frequency together with a percentage and a 95% CI.

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

A Nominal pressure is in the interval 80mmHg ± 7mmHg

B Dressing wear time is 7 days

C No leakage

The Composite Clinical Success (CCS) will be reported as a count and percentage with a 95% CI.

New text:

- Pressure maintenance at nominal 80mmHg

The following hypotheses will be tested to establish equivalence of the [redacted] system compared to the internally derived value, with equivalence margin, $\delta_1>0$:

$H_0: \pi - \pi_0 \geq \delta_1$
$H_a: \pi - \pi_0 < \delta_1$

In the stated hypotheses, μ represents the assumed mean operating pressure (80.2 mmHg) and μ_o represents the mean [redacted] pump operating pressure. The equivalence limit δ_1 = 7mmHg was chosen as a conservative non-clinically significant difference assuming that the difference is actually 0. The hypothesis will be tested by two-one-sided t-test (TOST) at the alpha level of 0.05. If the null hypothesis is rejected, equivalence will be confirmed. A two-one sided t-test and corresponding CI will be used to evaluate this hypothesis.

- Dressing wear time (7 days) as assessed through a combination of; data from device [redacted] and CRF recorded data of any unplanned dressing change.

The following hypotheses will be tested to establish equivalence of the [redacted] system compared to the literature derived value, with equivalence margin, d1>0:

$H_0: \pi - \pi_0 \geq \delta_1$
$H_a: \pi - \pi_0 < \delta_1$

In the stated hypothesis, μ represents the assumed mean dressing wear time in days and μ_o represents the mean [redacted] pump dressing wear time. The equivalence margin is 2.4 days. A two-one sided t-test with alpha = 0.05 will be used to evaluate the hypothesis. A binary variable accounting for below 7 days wear off time will also be used and the

proportion wearing of before 7 days will be reported as a percentage along with corresponding confidence interval. If necessary and if data allows, important associated factors will be adjusted for in a logistic model.

- Exudate management assessed by no occurrence of exudate leaks as assessed through a combination of leakage alert data from device [redacted] and/or clinical data on any leakage observed during the dressing wearing period resulting or not, in an unplanned dressing change

The following hypothesis will be tested to establish the non-inferiority of the [redacted] system exudate management to the literature derived value of 85% with non-inferiority margin, d1>0:

H_0: $\pi - \pi_0 \geq \delta_1$
H_a: $\pi - \pi_0 < \delta_1$

tin

In the stated hypothesis, π represents the assumed proportion of exudate managed through evaporation and π0 represents the mean [redacted] pump proportion of exudate managed through evaporation. The non-inferiority margin is 10%. An Exact test for non-inferiority of the study proportion to the literature derived 85% assuming a non-inferiority limit of -10%. A binary variable also for the leakage will also be used and the proportion of reported/identified leaks will be presented as a frequency together with a percentage and a 95% CI.

The logistic model will be used to evaluate the adjusted and the un-adjusted models for the CCS primary outcome variable. The variables considered important and to be included in the final model are Age, Diabetic status and the presence of any other co-morbidity as a binary variable. All other baseline and medical factors collected at baseline will be evaluated for importance in adjusted models and only those statistically significant in an un-adjusted model will be considered in the final model. Composite Clinical Success (CCS) defined as a binary variable (1/0) (1 if all three of the following are true and 0 if at least one of the three is false):

A Nominal pressure is in the interval 80mmHg ± 7mmHg

B Dressing wear time is 7 days

C No leakage

The Composite Clinical Success (CCS) will be reported as a count and percentage with a 95% CI.

Analysis of Secondary Endpoints Section 10.4.2

Old text:

Clinical efficacy and safety of the [redacted] NPWT system over a 30 day follow-up period to include:

- Incidence of Surgical Site Infection (SSI) – Superficial, deep, organ [CDC criteria] within 30 days of surgery
- Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep/organ.), seroma, necrosis, hematoma, suture abscess] within 30 days of surgery
- Percentage of skin graft take at Days 7, 14 and 30 as assessed by clinician visual assessment
- Condition of peri-wound skin and skin under the [redacted] assessed through visual inspection at 7, 14 and 30 days.
- Level of pain during wear of the [redacted] system, and at dressing removal assessed by VAS scale following 7 day therapy
- Level of pain during dressing removal (VAS scale) - pain intensity as none, mild, moderate, or severe.

For incidence of SSI and incidence of SSC binary variables indicating presence of/absence of will be defined and the frequencies together with percentages reported/identified outcomes will be reported. Logistic models will be fitted and important associated factors adjusted for if there is adequate data.

Summary statistics for all other secondary variables will be given according to the nature of the variable, continuous or categorical. For categorical 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. 95% confidence intervals will be reported where appropriate.

New text

Clinical performance and safety of the [redacted] NPWT system over a 30 day follow-up period to include:

- Incidence of Surgical Site Infection (SSI) – Superficial, deep, organ [CDC criteria] within 30 days of surgery
- Incidence of Surgical site Complications (SSC) [as applicable: dehiscence (superficial/deep/organ.), seroma, necrosis, hematoma, suture abscess] within 30 days of surgery
- Percentage of skin graft take at Days 7, 14 and 30 as assessed by clinician visual assessment
- Condition of peri-wound skin and skin under the pump [redacted] assessed through visual inspection at 7, 14 and 30 days.
- Level of pain during wear of the [redacted] system, and at dressing removal assessed by VAS scale following 7 day therapy
- Level of pain during dressing removal (VAS scale) - pain intensity as none, mild, moderate, or severe.

For incidence of SSI and incidence of SSC binary variables indicating presence of/absence of will be defined and the frequencies together with percentages reported/identified outcomes will be reported. The logistic model will be used to evaluate the adjusted and the un-adjusted models for the secondary variables, the incidence of surgical site infections, incidence of surgical complications and skin graft take. The variables considered important and to be included in the final model are Age, Diabetic status and the presence of any other co-

morbidity as a binary variable. All other baseline and medical factors collected at baseline will be evaluated for importance in adjusted models and only those statistically significant in an un-adjusted model will be considered in the final model.

Summary statistics for all other secondary variables will be given according to the natture of the variable, continuous or categorical. For categorical 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. 95% confidence intervals will be reported where appropriate.

Study Design Section 8.1

The text, "It is anticipated that up to 16 sites will participate within the UK and EU." has been changed to, "It is anticipated that up to 8 sites will participate within the UK and EU."

22.9 Protocol Amendment 1

22.9.1 General Purpose

This minor amendment was completed following initial ethical review of the protocol.

22.9.2 Rationale

The ethics committee stipulated that adults with reduced capacity and emergency cases are not needed for valid study data in this study. Therefore a minimum of 24 hours consideration should be given for informed consent and the reference to 2 hours consideration time must be removed.

22.9.3 Effect on Study Status

Not applicable; this amendment is to be in effect and implemented prior to subject enrollment.

22.9.4 Details

This amendment specifically revised the protocol as follows:

Informed consent

The text,

"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.

In the case of vulnerable subjects, the ICF must be understood and signed by the subject's legally authorized representative (parent or legal guardian). If the legally authorized representative is unable to read/write a witness signature is required as described previously.

All subjects will be given time to consider participation following the explanation of the study/reading of the patient information sheet. If the surgery is not considered emergency then at least 24 hours is preferred. If less than 24 hours is needed due to an emergency then the subject may be consented a few hours after explanation of the study is given. No true emergency cases (where the subject is unconscious or does not have time to consider the study) will be consented for this study",

was changed to,

"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 ample time (at least 24 hours) to consider participation following the explanation of the study/reading of the patient information sheet."

22.10 Instructions for Use

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

22.11 Principal Investigator Obligations (ISO 14155:2020)

1. General:

   The role of the principal investigator is to implement, oversee the management of 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. The principal investigator is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may delegate tasks to qualified members of the investigation site team but retains responsibility for the clinical investigation (see also 7.6 of ISO14155:2020). This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall implement procedures to ensure the integrity of all tasks performed and any data generated by this external organization.

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 document; evidence of such qualifications of the principal investigator shall be provided to the sponsor through up-to-date CVs or other relevant documentation,

NOTE National regulations can also apply.

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 can 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,
b. has an investigation site team that is: qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this document; evidence of such qualifications for members of the investigation site team shall be documented through up-to-date CVs or other relevant documentation,

NOTE National regulations can also apply.

c. has adequate facilities.

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 EC,
b. comply with the requirements described in 5.6 of ISO 14155:
c. obtain the written and dated approval/favourable opinion of the EC for the clinical investigation, and ensure that regulatory authority approval is provided by the sponsor and communicated to the EC where required, before recruiting subjects and implementing all subsequent amendments, if required,
d. perform safety reporting as specified in 10.8 (for adverse event categorization, see Annex F),
e. promptly report any deviations from the CIP 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 EC or the CIP,

NOTE National regulations can also apply.

f. notify suspension, premature termination, or routine close-out of the clinical investigation as described in Clause 8.

In particular circumstances, the communication with the EC 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 principal investigator shall

a. comply with the requirements specified in 5.8,
b. ensure compliance with ethical principles for the process of obtaining informed consent, and
c. ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.
NOTE Regulatory requirements can apply.

6. Compliance with the protocol.

The principal investigator shall:

a. indicate his/her acceptance of the CIP in writing,
b. conduct the clinical investigation in compliance with the CIP,
c. create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits as well as maintain documentation of the type and location of these source documents,
d. ensure that the investigational device is used solely by authorized users as specified in 7.2, and in accordance with the CIP and instructions for use,
e. propose to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device,
f. refrain from implementing any modifications to the CIP without agreement from the sponsor, EC and regulatory authorities, if required,
g. document and explain any deviation from the approved CIP 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 CRFs and in all required reports,
k. maintain the device accountability records,
l. comply with the procedure for the safe return of investigational devices including potentially hazardous devices, and in case of reported device deficiencies, collaborate with the sponsor to provide the necessary information allowing an accurate analysis where appropriate,
m. allow and support the sponsor to perform monitoring and auditing activities,
n. be accessible to the monitor and respond to questions during monitoring visits,
o. determine the cause and implement appropriate corrective and preventive actions to address significant noncompliance,
p. allow and support regulatory authorities and the EC when performing auditing activities,
q. ensure that all clinical investigation-related records are retained as specified in 8.3,
r. sign the clinical investigation report, as specified in 8.4.

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, as described in the informed consent,
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 can 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, provide subjects enrolled in the clinical investigation with some means of showing their participation, 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 the subject's personal physician about the subject's participation in the clinical investigation,

NOTE National regulations can apply.

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 (adverse event categorization, see Annex F),
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 CIP,

c. report to the EC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the CIP or by the EC,

NOTE 1 National regulations can also apply.

d. report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect,

NOTE 2 National regulations can apply.

e. supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

7

22.12 ASA Physical Status Classification System

Developed By: *ASA House of Delegates/Executive Committee*

Last Amended: *December 13, 2020 (original approval: October 15, 2014)*

ASA PS Classification	Definition	Examples, including, but not limited to:

ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the

[redacted]

		face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

* The addition of E denotes emergency surgery: (an emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

22.13 MHRA No Objection

Medicines & Healthcare products Regulatory Agency

MHRA

[redacted]
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HU3 2BN
UK

MHRA
10 South Colonnade
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London
E14 4PU
United Kingdom

www.gov.uk/mhra

25/01/2019

Our ref: CI/2018/0073

Dear [redacted]

CLINICAL INVESTIGATION: NO OBJECTION

Manufacturer : Smith & Nephew Medical Ltd
Model Number : n/a
Description : [redacted] system is a sterile, single-use, [redacted] Negative Pressure Wound Therapy dressing

I hereby notify you that the UK Competent Authority has no grounds for objection to the making available of the above medical device for the purposes of a clinical investigation as declared in the above notification.

Competent Authority Comments

Please ensure that you note and understand the requirements set out below for reporting adverse events to the UK Competent Authority. In addition please submit summary SAE reports quarterly.

Each of the study endpoints must be compared to a like for like comparator with data from the scientific community.

When the study has recruited 22 patients in each group who have completed the follow up period for each of the two groups, the applicant is requested to pause the trial and provide MHRA a comparative analysis for each endpoint succinctly with published literature pooled from a minimum of 5 research articles.

A descriptive analysis for each patient's consultant experience of the device is required and how each patient perceives the device in general.

In addition to the above, for knees a comparison with a standard dressing is required for range of movement (degrees of flexion and extension) at the final day follow up period. This new device may potentially inhibit the full benefits of a knee replacement with respect to range of motion due to the [redacted] system. It is important to emphasise confounding factors for example such as age, BMI and pre-operative range of movement could influence the results and hence a like for like comparison is essential.

MHRA will inform the outcome once a review has been carried out for the above data.

The device(s) must be labelled "*exclusively for clinical investigations*".

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Medicines & Healthcare products Regulatory Agency

MHRA

Please ensure that all requirements listed in the appendix to this letter are understood and adhered to.

Yours sincerely

[redacted]
(on behalf of the Competent Authority, UK)

[redacted]