Negative pressure wound therapy (PREVENA) versus standard dressings for incision management after renal transplant: a multicentre, partially-blinded randomised controlled trial

Incision Management with Prevena After Renal Transplant (IMPART-TRIAL)

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

Contents

Protocol Signature Page

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Protocol Signature page – All Investigators

I have read this protocol and agree to adhere to, the protocol, the local IRB/IEC regulatory requirements and the ICH Harmonised Guideline Integrated Addendum To ICH E6(R1): Guideline For Good Clinical Practice: E6(R2)

I will provide copies of this study protocol and all necessary information about this study to the study staff under my supervision.

I will discuss this material with them and ensure they are fully informed about the device under investigation as well as the aspect concerning the conduct of the study.

Investigator

Name: _____

Institution: _____

Address: _____

Phone: _____

Email: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

Title	Incision Management with Prevena After Renal Transplant (IMPART-TRIAL)
Objectives	Primary: The primary objective of this study is to determine if the Prevena Incision Management System reduces wound complications at the surgical site following renal transplant, when compared to standard dressings. Secondary: Secondary objectives of this study include identification of risk factors for wound complications at the surgical site, as well as reoperation, prolonged hospital stay, allograft survival, delayed graft function. This study will also assess pain, scar healing and quality of life in each treatment arm, and aim to complete a cost-benefit analysis of the Prevena device in renal transplantation.
Study Design	This study is a multicentre, partially-blinded randomised controlled trial, with site stratified block randomisation and partial blinding of outcome assessments. Patients undergoing a renal transplant will be allocated to one of two treatment arms, where either a Prevena device of appropriate size or standard dressing is applied to the closed incision. In the case that a patient requires bilateral incisions, both incisions will be allocated to the same treatment arm and counted as a single incision.
Planned Sample Size	250 participants each arm (500 total)
Selection Criteria	All patients presenting for a renal transplant over a 24 month period at one of the participating sites will be eligible for enrolment in this study. Only participants who give informed consent will be enrolled in the study.
Study Procedures	Participants will be randomised to either a Prevena (intervention arm) or standard dressing (control arm) is placed on the closed incision after renal transplantation. Monitoring will occur daily during hospitalization and up to 30 days postoperatively to review any wound complications, with subsequent assessment at 90 days.
Statistical Procedures and Analysis Plan:	Statistical analysis will be pre-specified and conducted according to both principles of intention of treat and per-protocol analysis, using SPSS version 20 (IBM, Armonk, NY, USA The Intention to Treat (ITT) sample will be based on all enrolled subjects, and the per-protocol analysis will be based on all patients who have a dressing placed on the closed incision following renal transplant. Each incision will be randomized to the Prevena or standard dressing group. In the case that a patient requires bilateral incisions, both incisions will be allocated to the same treatment arm and counted as a single incision. Baseline characteristics of the two groups will be recorded and compared using Student's t-test and chi-square test for continuous and discrete data respectively. The primary outcome, the proportion of wound complications, will be compared between the Prevena and standard dressing groups using a chi-square test without Yates' continuity correction with a two-sided alpha of 0.05 at the final analysis using the Peto approach to preserve the overall

	significance level of 0.05 (23). Patients lost to follow-up will be used in an intention-to-treat analysis with last observation carried forward The secondary outcome of identification of risk factors for wound complications will be assessed by multiple logistic regression of collected variables to assess their odds ratio.
Sample Size Calculation:	Wound infection rates have been estimated between 5 and 30% based on current literature, including a systematic review and meta-analysis.(3)(10) Weighting the participating site's preliminary audit data by expected enrolment rates, the average wound complication rate was estimated to be 15%. NPWT has been suggested to offer an approximate 46% reduction in wound infection rates for abdominal incisions (3)(10). Based on a type one two-sided error of $\alpha = 0.05$ and a type two error of $\beta = 0.2$ (corresponding to a power of 80%) a total sample size of 239 patients per group (478 in total) is needed to evaluate primary endpoints, which was calculated using the power formula for a chi-square test without Yates' continuity correction due to the large sample size and binary dependent variable (17). Accounting for potential loss to follow up, the sample size has been rounded up to 250 per arm (500 total).
Duration of the study	24 months

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
CNC	Clinical Nurse Consultant
NPWT	Negative Pressure Wound Therapy
Prevena	PREVENA Incision Management System
SD	Standard (waterproof, adhesive) Dressings
RT	Renal Transplant
RNSH	Royal North Shore Hospital; Sydney, Australia
RPAH	Royal Prince Alfred Hospital; Sydney, Australia
WH	Westmead Hospital; Sydney, Australia
HD	Haemodialysis
PD	Peritoneal dialysis
LOS	Length Of Stay
EC	Ethics Committee
PISCF	Patient Information Sheet and Consent Form
ITT	Intention to Treat
IFU	Instructions for Use
EQ-5D-5L	A Quality of life standardised instrument developed by the EuroQol Group
NRS	Numerical Rating Scale
POSAS	The Patient and Observer Scar Assessment Scale
MCS	Microscopy, Culture and Sensitivity
REDCap	Research Electronic Data Capture

1. STUDY MANAGEMENT

1.1 Principal Investigator

Dr Christopher Selvaraj, RNSH

1.2 Chief Investigator

Dr Vikram Puttaswamy, RNSH

1.3 Associate Investigators

Dr Cindy Wang; RNSH
Dr Jerome Laurence; RPAH
Dr Henry Pleass; Westmead Hospital

1.4 Statistician

Statisticians will be based in the Surgical Education, Research and Training (SERT) Institute at Royal North Shore Hospital.

1.5 Sponsor

Northern Sydney Local Health District

1.6 Funding and resources

Internal funding from each centre.

2. INTRODUCTION AND BACKGROUND

2.1 Background Information

Renal transplantation is considered to be the best treatment option for patients with end stage kidney disease in terms of quality of life and survival outcomes, as well as relative cost efficiency compared to dialysis.(1) Transplant recipients are susceptible to wound complications, arguably the most common post-transplant surgical complication, which may contribute to an additional risk of graft rejection or failure, prolonged length of stay, readmission and re-operation, as well as increased treatment costs. (2)

Wound complications have been previously superficial or deep dehiscence and/or infection, perigraft collections or seromas, cellulitis, lymphocoeles, and prolonged wound drainage. Studies have shown that the most important risk factors for wound complications in transplantation are immunosuppression and obesity (3). The incidence of wound infection in the presence of immunosuppression is approximately 7%, and more potent immunosuppressive agents are thought to result in a higher incidence of wound complications. (4) Comparing patients with high (>30) and low BMI (<30) patients, meta-analyses have demonstrated a significantly higher risk of wound infection (RR = 3.13, CI, 2.08–4.71; P <0.001), and wound dehiscence (RR 4.85, CI, 3.25–7.25; P <0.001). (5)(6)

Other relevant factors in renal transplantation include surgical technique and expertise, reoperative procedures, the presence of a haematoma, as well as recipient comorbidities such as advanced age, diabetes, malnutrition, dialysis (haemo- and peritoneal), and prolonged uraemia. The surgical closure technique of the incision, in particular, the precise closure of defects in each layer, has also been identified as an independent factor in reducing wound complications. (7) (8)

Negative pressure wound therapy (NPWT) utilises a foam sponge, in combination with a semipermeable adhesive dressing and a vacuum pump device to increase blood flow, drain fluid and exudate, and contract wound edges. Meta- analyses have suggested that when compared to standard wound dressings on closed incisions, NPWT significantly decreases wound size and healing time, with a significant reduction of risk of surgical site infections (RR=0.54, p= 0.01), and a significant reduction in risk of seroma formation (RR=0.48, p=0.01). (9) (10) (11).

In high risk wounds following cardiac and orthopaedic surgery, NPWT has been used safely without complications. (12) (13) Furthermore, international studies have demonstrated through cost-utility analysis that closed-incision negative-pressure therapy is likely a cost-saving technology when used in high-risk patients following abdominal incisions. (14)

2.2 Research Question

In patients undergoing a renal transplant (RT), does the application of negative pressure wound therapy (NPWT) with a Prevena Incision Management System (Prevena) immediately to the closed wound at the end of the renal transplant operative procedure result in fewer wound complications, when compared to standard adhesive, waterproof dressings (SD)?

2.3 Rationale for Current Study

The Prevena Incision Management System (Prevena; Kinetic Concept Inc. San Antonio, Texas, United States) is a portable NPWT device, utilising a foam interface containing 0.019% ionic silver. Since the first published case of its use in renal transplantation in 2015, a systematic review the following year concluded that the Prevena had been successfully used following renal transplantation to heal infected and dehisced wounds, as well as lymphocoeles and urine leaks. (15)(16)

Due to the multifactorial nature of wound complications following renal transplantation, controversy still exists regarding the utility of preventative management of wound complications, and current literature has identified a further need for robust evidence regarding the safety and efficacy of NPWT in renal transplantation, ideally in the form of a randomised controlled trial. (3)(10) (16)

This study is a multicentre, partially-blinded, randomised controlled trial of the Prevena Incision management system versus standard adhesive, waterproof dressings on closed-incisional wounds following renal transplantation, to evaluate outcomes on wound healing in the postoperative period.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to determine if the Prevena Incision Management System reduces all possible wound complications at the surgical site following renal transplant, when compared to standard dressings.

3.2 Secondary Objectives

Secondary objectives of this study include identification of risk factors for wound complications at the surgical site, as well as reoperation, prolonged hospital stay, allograft survival, delayed graft function. This study will also assess pain, scar healing and quality of life in each treatment arm, and aim to complete a cost-benefit analysis of the Prevena device in renal transplantation.

4. STUDY DESIGN

4.1 Type of Study

This study is a multicentre, partially-blinded, randomised controlled trial, with site stratified block randomisation and partial blinding of outcome assessments. Patients undergoing a renal transplant will be allocated to one of two treatment arms, where either a Prevena or standard dressing is applied to the closed incision.

4.2 Study Design

Ethics approval will be obtained from SLHD-RPA by the Lead site at RNSH. All sites will require Governance approval prior to study commencement. Enrolled participants in this study will present for renal transplantation at a participating study site, having received routine planning and workup for the operation which will include education regarding the trial, and providing informed consent at the time of admission for the operation. Study investigators will register the patient in an online database (REDCap Database Vanderbilt University) controlled by the study investigators, which will randomly allocate the patient to a treatment arm, to be revealed after transplantation and during the closure procedure (closure defined as closure to the muscle, subcutaneous tissue or skin). Patient data variables including demographic data, medical comorbidities and pathology results will be recorded from the patient electronic medical record (see appendix). Details of the donor kidney will be also be recorded, including donor demographics, anatomical characteristics, ischaemic time, and time of retrieval.

The patient will be prepared for surgery as per site specific protocols; variables to be recorded include peri operative antibiotic administration and skin preparation (application of an antiseptic agent such as chlorhexidine or iodine, or iodine impregnated drapes). Each surgeon will proceed with the procedure of renal transplantation as per operator preference. Operative details to be recorded include site and side of incision (Rutherford-Morrisson), warm ischaemic time, time of reperfusion, operation duration, estimated blood loss, length of incision, and method (materials; eg. sutures, staples) of closure in layers (muscle, subcutaneous tissue and skin). Drain presence and placement is also recorded. Bilateral renal transplants and bilateral incisions will be counted as one incision and will allocated to the same treatment arm as one entity.

The intervention arm will have the closed incision dressed with the Prevena Incision Management System (Kinetic Concepts Inc, San Antonio, TX, USA), a portable NPWT device, utilising a foam interface containing 0.019% ionic silver. The Prevena is preset to a continuous vacuum suction at 125mmHg. The Prevena device of appropriate size is to be applied under sterile conditions at the time of closure of the incision, with drain placement to be >10cm from the wound edge. The device should remain intact for a total of 7 days, at which point it will be removed. The wound will be inspected by a study investigator for evidence of a wound complication. A dressing may be reapplied, including a Prevena dressing if thought clinically indicated by the presence of a wound complication.

Postoperative ultrasound of the grafted kidney may be performed by peeling back the adhesive component of the Prevena dressing, and the Prevena can be subsequently reinforced with an adhesive dressing to establish adequate seal, with suction reinitiated within one hour if lost. If the wound edge is exposed, the Prevena device is inadvertently removed during ultrasound or clinician concern regarding the wound or device results in removal of the Prevena device earlier than planned, the device can be replaced at investigator discretion, however these details must be documented in the database. The patient will continue in the intervention arm as per principles of intention to treat regardless of whether the Prevena is replaced.

The control arm will have the closed incision dressed with a standard waterproof, adhesive dressing at the operator's discretion. This will not be controlled, but the type of dressing used will be recorded. This dressing will remain intact for a minimum of 7 days and may be changed thereafter as per site specific practices, which will be documented.

The perioperative recipient management will otherwise be identical in both the intervention and the control arms and guided by site specific protocols. Data will be recorded daily until the date of discharge regarding site specific practices in regard to immunosuppression, antibiotics, imaging, drain management, and pathology results. If the patient is discharged with a drain, volumes must be recorded till the date of removal. If the patient re-presents to hospital with a wound complication, requires a re-operation or subsequent interventions, this is recorded for the requisite primary and secondary endpoints by the study investigators.

All patients will follow up at time points below, for assessments of the surgical site and overall health (see appendix). The date of drain removal and volumes drained will be confirmed and recorded if the patient was discharged with a drain. On review, patients may also undergo an ultrasound, or other suitable imaging at investigator discretion, to determine the presence of deep wound complications. Imaging staff to will be blinded to the patients allocated treatment arm in the trial.

The timeline for patient follow up and assessment is as follows:

Day 7 – The dressing is taken down for review and not replaced unless indicated. The review will include a microbiology swab (MCS), photo of the wound, modified ASEPSIS wound assessment, a pain assessment (NRS) and patient quality of life questionnaire (EQ-5D).

Day 14 – The dressing is taken down for review and not replaced unless indicated. The review will include a microbiology swab (MCS), photo of the wound, modified ASEPSIS wound assessment, a pain assessment (NRS), and quality of life questionnaire (EQ-5D).

Day 30 (+/- 3 days) – The patient will present for follow up for an extended wound review by a study clinician or wound CNC, and a vascular sonographer. The review will include a modified ASEPSIS wound assessment, a photo of the wound, a pain and scar assessment (POSAS), a quality of life questionnaire (EQ-5D), and an ultrasound of the transplanted kidney which will also identify deep wound complications.

90 days (+/- 3 days) – The patient will present for follow up for wound review and ultrasound, which will include a photo of the wound, a scar assessment (POSAS), a quality of life questionnaire (EQ-5D), and an ultrasound of the transplanted kidney which will also identify deep wound complications.

4.3 Number of Participants

Expected number of participants is 500, with approximately 250 patients allocated to each arm.

4.4 Study sites

The study sites are Royal North Shore Hospital, Royal Prince Alfred Hospital and Westmead Hospital, located in Sydney, Australia. Outside the confines of this research protocol, surgeons at each site will perform the renal transplantation as per their own procedural methodology, and perioperative management will be as per site specific protocol and guidelines.

4.5 Expected Duration of Study

The study is expected to commence in January 2019 and conclude in 2021.
Expected duration of recruitment is 24 months and planned duration of follow up is 90 days.

4.6 Primary and Secondary Outcome Measures

Primary outcomes of this study include wound infection, wound dehiscence or fluid collection at the surgical site within 30 postoperative days (see Appendix for Classification of wound complications)

Secondary outcomes include pain, scar healing, quality of life, reoperation, duration and volume of wound drainage, graft function, hospital length of stay, clinical adverse events and mortality (see Appendix for NRS, POSAS, EQ 5D-5L and List of dependent variables).

5. PARTICIPANT ENROLLMENT AND RANDOMISATION

5.1 Recruitment

All patients presenting for a renal transplant over a 24 month at one of the participating sites will be eligible for enrolment in this study. Only participants who give informed consent will be enrolled in the study, and this will be done by a study investigator. Participants may be recruited at any point after written informed consent, prior to surgery.

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

The participant:

1. is an adult ≥ 18 years old, regardless of comorbidities or BMI
2. is able to provide their own informed consent
3. will undergo open renal transplant surgery, including those who undergo dual renal transplant or simultaneous pancreas transplant.
4. will require a surgical incision(s) likely to be able to be covered completely by one or more Prevena Incision Management Systems.
5. is willing and able to return for the required follow up assessments.
6. if concurrently enrolled in a clinical trial it must not impact on patient health or the surgical incision site and the study must be documented

5.2.2 Pre-Operative Exclusion Criteria

The participant:

1. has a known allergy or hypersensitivity to silver, or drape materials that contain acrylic adhesives.
2. Is not suitable for closure of the surgical wound, and as such the wound must be left open or an open NPWT device is required.
3. Is not willing to comply with the study procedures.

5.2.3 Intra-Operative Exclusion Criteria

The participant:

1. Has an unforseen intraoperative event mandating additional management including a planned re-exploration.
2. Has obvious intraoperative contamination of the surgical site.
3. Has a wound with suspected ischaemia in the incision area, or inadequate haemostasis.
4. Requires drains that cannot be covered by the Prevena dressing.

5.3 Informed Consent Process

Informed consent should be obtained in accordance with the applicable regulations, and current versions of Declaration of Helsinki, ICH-GCP and ISO 14155. If a patient might be eligible for the study, a study investigator may approach them to obtain the written informed consent. During the consent process, the background of the proposed study including the benefits and risks of study participation should be explained in detail to the patient.

It has to be emphasized that a patient's participation in the trial is voluntary and that the patient may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the patient is otherwise entitled. The patient must be given ample time to read the patient information and to address questions before signing the consent form. Study information and a copy of the Ethics Committee approved consent form will be signed (by the Investigator and participant). Patients are considered provisionally enrolled in the study once they have signed the Consent Form. Enrolled participants should be treated within 30 days from the day of Consent. If the index procedure is not performed within 30 days of the provisional enrolment the participant must be re-screened and written informed consent re-obtained.

5.4 Enrolment and Randomisation Procedures

All patients presenting for a renal transplant over a 24 month period at one of the participating sites will be eligible for enrolment in this study. Patients who sign the Participant Information Sheet and Consent Form (PISCF) and fulfil all inclusion and exclusion criteria, as well as compliance with contraindications listed in the Prevena IFU, will be considered eligible for study participation. Participants may recruited at any point prior to surgery once surgery is confirmed, ideally at the time of admission to hospital for the procedure, or if this is not possible, at the time consent is obtained for the surgery. A unique study identification number is then assigned to enrolled participant by the study investigators.
Participants who signed the PISCF but do not fulfil all inclusion and exclusion criteria, IFU related indications and contraindications, hospital standard of care tests, or who withdraw informed

consent prior to the procedure are screen failures. They will be documented on the screening and enrolment log with the screening failure reason. For the purposes of analysis, an Intention to Treat (ITT) sample will be based on all enrolled subjects, and a secondary as per-protocol analysis will be based on all patients who have the intervention of having a dressing placed on the closed incision following renal transplant.

Patient registration will occur prior to surgery on an online research database (REDCap; Vanderbilt University, Nashville, USA) hosted at Royal North Shore Hospital (19). Randomisation via REDCap will occur when the patient fulfils all intra-operative exclusion criteria and after commencement of skin closure (defined as closure to the muscle, subcutaneous tissue and skin). Randomisation will be stratified by site, with block randomisation by variable block size in a 1:1 ratio. , The surgical team, clinical staff, and patient will not be blinded to the intervention status.

5.5 Blinding Arrangements

Study investigators will be partially blinded, as surgical proceduralists and treating clinical staff will be unable to be blinded due to the visually distinct difference between a Prevena and standard dressing. Study investigators will be able to identify the allocated treatment within 7 days due to active intervention and likely at 14 days due to ongoing clinical contact. However, wound assessment at Day 7 and Day 14 (as well as Day 30 and 90) will include a photo of the wound by a study investigator once the dressing is removed, for independent blinded assessment by the designated wound assessor for each site (or alternative site for Day 30 and 90 photos); this is done to improve the validity of assessment. Blinding will occur at Day 30 and 90 follow up for imaging staff and the designated independent wound assessor for each site, who will not be informed of the allocated treatment arm. Patients will be instructed to not disclose this information to the wound assessor or imaging staff.

5.6 Participant Withdrawal

5.6.1 Reasons for withdrawal

Patients may withdraw from the study at any point, but will continue to be followed up and managed as per routine practice. Patient withdrawal may also occur due to loss of follow up, adverse event or death. Investigators may withdraw the patient from the study once the patient has been randomised, if the Investigator believes the allocated treatment arm is not in the patient's best interests, or the patient meets IFU related contraindications, however the reasons for withdrawal must be clearly documented.**5.6.2 Handling of withdrawals**

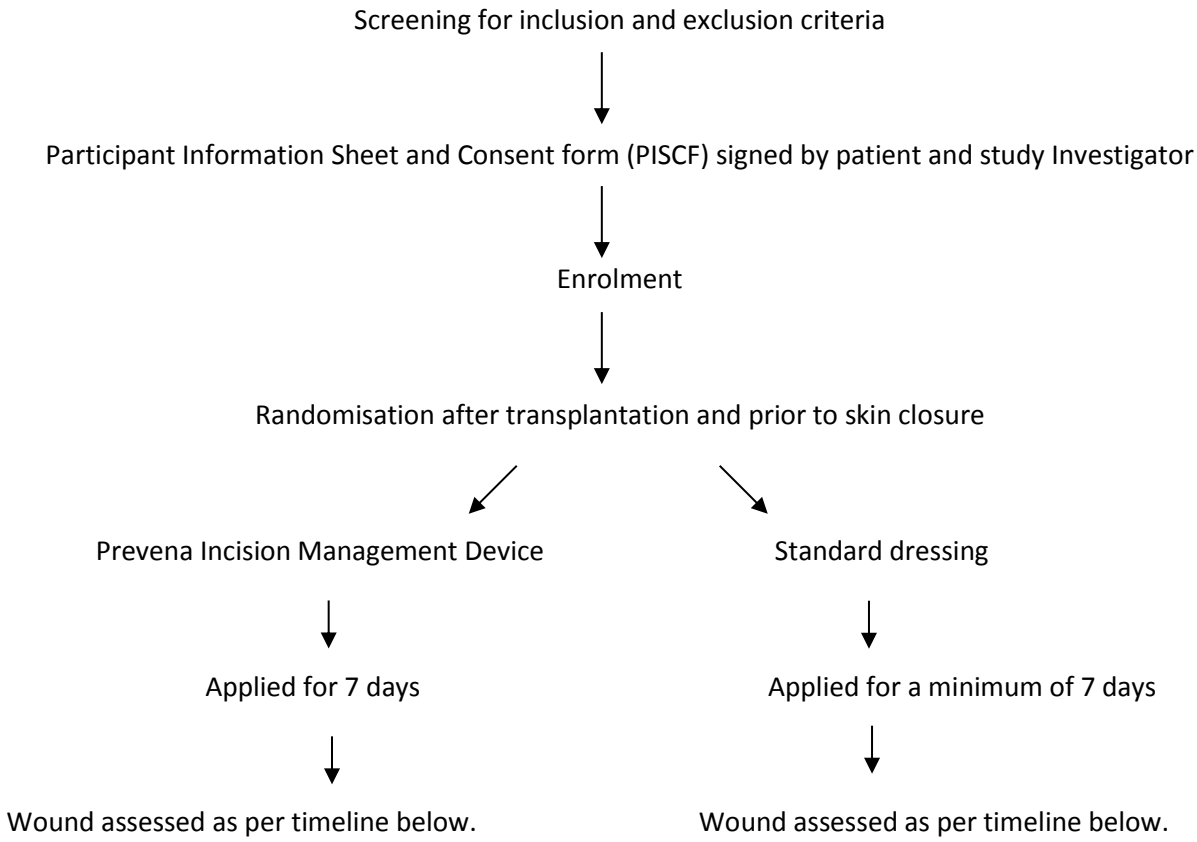
All participants withdrawn will ideally complete all study visits including Day 30 follow-up if able, as per routine clinical practice. Withdrawn patients will be included in an intention to treat analysis.

5.6.3 **Study Closure**

Participants will be informed of study closure and will continue follow up as per routine clinical practice post transplantation.

6 STUDY VISITS AND PROCEDURES SCHEDULE

Study Flow Chart



Timeline for follow up wound assessments:

Day 7 – The dressing is taken down for review and not replaced unless indicated. The review will include a microbiology swab (MCS); photo of the wound; modified ASEPSIS wound assessment; a pain assessment (NRS) and patient quality of life questionnaire (EQ-5D).

Day 14 – The dressing is taken down for review and not replaced unless indicated. The review will include a microbiology swab (MCS); photo of the wound; modified ASEPSIS wound assessment; a pain assessment (NRS) and the quality of life questionnaire (EQ-5D).

Day 30 (+/- 3 days) – The patient will present for follow up for an extended wound review by a study clinician or wound CNC, and a vascular sonographer. The review will include a modified ASEPSIS wound assessment; a photo of the wound; a pain and scar assessment (POSAS); a quality of life questionnaire (EQ-5D and an ultrasound of the transplanted kidney which will also identify deep wound complications.

Day 90 (+/- 3 days) – The patient will present for follow up for wound review and ultrasound, which will include a photo of the wound; a scar assessment (POSAS); a quality of life questionnaire (EQ-5D) and an ultrasound of the transplanted kidney which will also identify deep wound complications.

Event	Day 0 Enrolment	Day 7	Day 14	Day 30 (+/- 3 days)	Day 90 (+/- 3 days)
Screening for Inclusion / Exclusion criteria	✓				
Participant Information Sheet and Consent Form (PISCF)	✓				
Routine perioperative data collection (Appendix C)	✓	✓	✓	✓	✓
Modified ASEPSIS wound assessment (Appendix B)		✓	✓	✓	✓
Photo of wound using REDCap App		✓	✓	✓	✓
Quality of life questionnaire (EQ-5D-5L) (Appendix D)		✓	✓	✓	✓
Microbiology swab (MCS)		✓	✓		
Pain Assessment (NRS) (Appendix G)		✓	✓		
Pain and Scar Assessment (POSAS) (Appendix E, F)				✓	✓
Ultrasound of Transplanted Kidney (Study specific)				✓	✓
Adverse Event & Serious Adverse Event Assessment		✓	✓	✓	✓

7. CLINICAL AND LABORATORY ASSESSMENTS

See Appendix C.

8. ADVERSE EVENT REPORTING

Adverse event reporting for clinical trials involving therapeutic products will meet the requirements of the National Health and Medical Research Council, Australian Health Ethics Committee (AHEC) Position Statement "*Monitoring and reporting of safety for clinical trials involving therapeutic products*" (May 2009), which can be found at:
www.nhmrc.gov.au/health_ethics/hrecs/reference/_files/090609_nhmrc_position_statement.pdf

8.1 Definitions

Adverse event

An adverse event for medicines is also referred to as an adverse experience, any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Devices Events

An adverse event for devices is any undesirable clinical occurrence in a participant whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

In relation to devices any adverse medical occurrences include: death and or a serious deterioration in health of a patient user or other. This would include:

- a life threatening illness or injury;
- a permanent impairment of body function or permanent damage to a body structure
- a condition requiring hospitalisation or increased length of existing hospitalisation
- a condition requiring unnecessary medical or surgical intervention or
- death or a serious deterioration in health had suitable action or intervention not taken place
- a malfunction of a device such that it has to be modified or temporarily/permanently taken out of service; or a factor (deterioration in characteristics or performance) found on examination of the device

8.2 Assessment and Documentation of Adverse Events

All adverse events (see Appendix C) will be documented in the study database.

8.3 Eliciting Adverse Event Information

Adverse events (see Appendix C) will be reviewed and confirmed at the follow up assessments.

8.3 Serious Adverse Event Reporting

8.3.1 SAEs

Serious adverse events will be recorded in the study data, and site-specific HREC reporting for incident and risk management will be followed.

Serious adverse event (SAE):
An unforeseen medical event that occurs in the course of clinical research that:

- results in participant death
- is life-threatening to the participant
- requires the inpatient hospitalisation or prolongation of existing hospitalisation and leads to the participant having a persistent or significant disability/incapacity.

8.3.2 SUSARs

Suspected Unexpected Serious Adverse Reactions (SUSAR) will be recorded in the study data, and site-specific HREC reporting for incident and risk management will be followed.

9 STATISTICAL METHODS

9.1 Sample Size Estimation

Wound infection rate have been estimated between 5 and 30% based on a current literature, including a systematic review and meta-analysis.(3)(10) Weighting the participating site's preliminary audit data by expected enrolment rates, the average wound complication rate was estimated to be 15%. NPWT has been suggested to offer an approximate 46% reduction in wound infection rates for abdominal incisions (3)(10).

Based on a two-sided type one error of $\alpha = 0.05$ and a type two error of $\beta = 0.2$ (corresponding to a power of 80%) a total sample size of 239 patients per group (478 in total) is needed to evaluate primary

endpoints, which was calculated using the power formula for a chi-square test without Yates' continuity correction due to the large sample size and binary dependent variable (22). Accounting for potential loss to follow up, which is estimated to be minimal, as every patient receiving a kidney transplant is planned to follow up every day for 30 days postoperatively, the sample size has been rounded up to 250 per arm (500 total). Missing data from patients who fail to have endpoints recorded will be treated on an intention to treat basis with last observation carried forward.

Estimated mean wound complication rate in control arm across 3 sites : 15%
Site 1 : 5-10% (60 transplants per year, audit data demonstrates 5% dehiscence rate)
Site 2 : 8-15% (90 transplants per year, audit data demonstrates 8% infection rate)
Site 3 : 18-25% (100 transplants per year, audit data demonstrates 18% dehiscence rate)
Conservative estimate of treatment effect: ~50% reduction in all wound complications with closed incision NPWT over lower abdominal/groin wounds (Rutherford Morrison) in high risk population.
Estimated complication rate for Prevena arm (intervention) = 7%

Dichotomous Endpoint, Two Independent Sample Study

Sample Size	
Group 1	239
Group 2	239
Total	**478**

Study Parameters	
Incidence, group 1	15%
Incidence, group 2	7%
Alpha	0.05
Beta	0.2
Power	0.8

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + kp_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.11 * 0.89 * (1 + \frac{1}{1})} + 0.84 * \sqrt{0.15 * 0.85 + (\frac{0.07 * 0.93}{1})} \right\}^2 / 0.08^2$$

$$N_1 = 239$$

$$N_2 = K * N_1 = 239$$

p_1, p_2 = proportion (incidence) of groups #1 and #2
$\Delta = |p_2 - p_1|$ = absolute difference between two proportions
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

Kane SP. Sample Size Calculator. ClinCalc: http://clincalc.com/stats/samplesize.aspx. Updated July 1, 2017. Accessed August 24, 2018.

9.2 Population to be analysed

Every patient presenting for renal transplant that meets the criteria for inclusion and exclusion will included for intention to treat analysis. Secondary analysis as per protocol will also be performed.

9.3 Statistical Analysis Plan

Statistical analysis will be pre-specified and conducted according to both principles of intention of treat and per-protocol analysis, using SPSS version 20 (IBM, Armonk, NY, USA). Each incision will be randomized to the Prevena or standard dressing group. In the case that a patient requires bilateral incisions, both incisions will be allocated to the same treatment arm and counted as a single incision. Baseline characteristics of the two groups will be recorded and compared using Student's t-test and chi-square test for continuous and discrete data respectively. The primary outcome, the proportion of wound complications, will be compared between the Prevena and standard dressing groups using a chi-square test without Yates' continuity correction with a two-sided alpha of 0.05 at the final analysis using the Peto approach to preserve the overall significance level of 0.05 (23). An absolute risk increase/reduction for wound complications will be presented for the use of Prevena, as well as the number needed to treat in order to prevent specific wound complications. Patients lost to follow-up will be used in an intention-to-treat analysis with last observation carried forward.

The secondary outcome of identification of risk factors for wound complications will be assessed by multiple logistic regression of collected variables to assess their odds ratio. To prevent overfitting with the selected sample size, variables will be stepwise selected and also assessed for multicollinearity with the significance level of the dependent variables adjusted for multiplicity. Secondary outcomes will be compared between groups using a chi-square or Fisher's test for reoperation rate and delayed graft function and t-test for continuous variables, including the pain scale and quality of life. Non-normally distributed continuous variables will be tested for and compared using the Mann–Whitney *U* test. Survival analysis will be performed for allograft survival time with subjects without events censored at the 90 day final observation. A *p* value of less than 0.05 will be considered significant for the secondary outcomes and all tests will be two-sided.

9.4 Interim Analyses

Interim review of recruitment will occur at the 6 month period, and interim analysis of preliminary data will occur at the 1 year mark. Sample size estimates will be reassessed given actual rates of enrolment after the 6 month period to ensure that the a priori sample size calculated is realistic, and the trial may be extended to allow for adequate patient recruitment. The trial will not be stopped for superiority reasons unless the adverse event rate and safety of the product is determined to be significant. Significance of the primary outcome will be assessed with an interim stopping level of p=0.001 using the Peto approach. (23)

10 DATA MANAGEMENT

10.1 Data Collection

Study data will be collected by study investigators using paper and electronic study data collection forms, the hospital based patient electronic medical record, and managed using REDCap electronic data capture tools hosted at Royal North Shore Hospital. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an

intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. (19) Photos of patients wounds will be uploaded to REDCap using the image upload survey tool, and should be taken from 20-30cm above the wound with a mobile phone utilising the REDCap mobile phone app. Wounds will not be marked or identified with unique patient identifiers, so care must be taken to ensure the photo is uploaded for the correct patient.

10.2 Data Storage

All electronic data will be stored on the secure online REDCap database at Royal North Shore Hospital. Only investigators and study staff will have their own password for access to this database. Passwords for the logins must not be shared, every person intending to enter data must contact the study coordinator at Royal North Shore Hospital to obtain their own log in. Any physical data will be stored within a locked room within the Research Units at each site and only study investigators will have access to this room.

10.3 Data Confidentiality

Re-identifiable coded data will be stored on our secure online REDCap database, accessible only by study investigators. Each site will be able to see only their own data except for Royal North Shore Hospital who will be managing the data. Relevant codes will be encrypted and stored on a hard drive in a locked room within Research Units at each site and only investigators will have access this room. The method of coding and data abstraction will be site specific, but controlled by the study investigators at RNSH.

10.4 Study Record Retention

After analysis of this data and the end of patient follow-up all electronic data from Royal North Shore Hospital, Royal Prince Alfred Hospital and Westmead Hospital will be stored securely at Royal North Shore Hospital in the Vascular Surgery Research Office and destroyed after 15 years in accordance with the Australian Code for the responsible conduct of Research, TGA ICH – GCP and the National Statement on Ethical conduct in Human Research.

11 ADMINISTRATIVE ASPECTS

11.1 Independent HREC approval

This study has been approved by the Sydney Local Health District HREC, reference number: X18-0513

11.2 Amendments to the protocol

Any amendments will be submitted to the HREC for review prior to implementation as per HREC guidelines.

11.3 Protocol deviations

Any protocol deviations will be submitted to the HREC for review.

11.4 Participant reimbursement

Participants will not be reimbursed in this study.

11.5 Financial disclosure and conflicts of interest

Nil disclosures or conflicts of interest

12 USE OF DATA AND PUBLICATIONS POLICY

Intention is to publish study results in a peer-reviewed academic journal. Study participants will be informed that academic journals are accessible to the public, and all published patient data associated with this study will be de-identified to ensure patient confidentiality.

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14 APPENDICES (A – G)

Appendix A. Classification of wound complications (adapted from Mehrabi et al (3), CDC guidelines; Horan et al (17))

1) Superficial wound dehiscence: A separation of the superficial layers (skin and subcutaneous tissues) in the absence of documented incisional infection.

(2) Deep wound dehiscence or fascial dehiscence: The separation of the muscular fascia of the incision in the postoperative period, requiring operative repair.

(3) Perigraft fluid collection/seroma: detected by clinical suspicion and confirmed by ultrasound or CT/MRI. Perigraft fluid collections are diagnosed when the location of the fluid is deep to the muscular fascia. A seroma is diagnosed when there is a sterile fluid collection superficial to the muscular fascia. Urine leaks are also recorded, and fluids can be identified through pathology testing.

(4) Superficial wound infection: Diagnosed within 30 days of operation, limited to skin or subcutaneous tissue, and at least one of the following should be present:
(a) purulent drainage from the superficial incision;
(b) a sign or symptom of infection, such as pain, tenderness, heat, or swelling.
(c) the diagnosis of superficial wound infection is confirmed by the surgeon.

(5) Deep wound infection: Diagnosed within 30 days of operation, involvement of the fascial or

muscular layers, and at least one of the following should be present:
(a) purulent drainage from the deep incision;
(b) spontaneous dehiscence while the patient has fever (>38_C), localized pain, or tenderness;
(c) An abscess is found on direct examination, on reoperation, or by radiologic examination; the content contains pus, and the culture yielded one or more micro-organisms;
(d) the diagnosis of deep incisional infection is confirmed by the surgeon.

(6) Cellulitis: Diagnosed by presence of erythema, tenderness, swelling and warmness of the skin surrounding the wound.

(7) Lymphocele: Deep lymphatic collections with pseudomembrane formation. The diagnosis is made by ultrasonography, CT or MRI and confirmed by needle aspiration of the lymphocele content and measuring the creatinine concentration or finding lymphatic components.

(8) Prolonged wound drainage: Defined as continuous fluid discharge greater than 50 mL/d through the drain or wound for more than seven days after transplantation during the first hospitalization. Fluids are identified by pathological testing at clinician discretion

Appendix B: Modified ASEPSIS Wound assessment form

Wound Assessment for patient Study ID _____ (de-identify patient to assessor)

Assessor_____

Wound site (please circle): Right Iliac Fossa/ Left Iliac Fossa/ Midline

Wound Length _____

Dressing type _____ (blinded to assessor)

Day _____ post op Date /Time _____	points
Skin ☐ Intact ☐ Minor/small separation or wound breakdown ☐ Major / complete wound breakdown	
Separation of Deep Tissue ☐ 0% of wound affected	0

☐ 1-20% ☐ 20-39% ☐ 40-59% ☐ 60-79% ☐ >/= 80%	2 4 6 8 10
Fascia intact ☐ Yes ☐ No	
For Wound Dehiscence Size: length x width x depth (mm) _____	
Signs of Inflammation	
Erythema ☐ 0% ☐ 1-20% of wound affected ☐ 20-39% ☐ 40-59% ☐ 60-79% ☐ >/= 80%	 0 1 2 3 4 5
Pain at wound site ☐ Yes ☐ No	
Exudate ☐ No (Dry) ☐ Yes (Moist)	0
Exudate Colour ☐ Serous (clear) ☐ Sanguineous (bloody) ☐ Serosanguinous (thin/pink) ☐ Purulent (thick opaque/green/brown)	
If serous: Exudate volume ☐ Scant (1-20% wound moist/ bandage most) ☐ Small/minimal (20-39%) ☐ Moderate (40-59%) ☐ Large (60-79%) ☐ Very large/Copious tissue filled with fluid (>80%)	 2 4 6 8 10
If purulent: exudate volume ☐ Scant (1-20% wound moist/ bandage most) ☐ Small/minimal (20-39%) ☐ Moderate (40-59%) ☐ Large (60-79%) ☐ Very large/Copious tissue filled with fluid (>80%)	 2 4 6 8 10

Odour ☐ No odour ☐ Malodorous	
Wound base ☐ Healthy – Red ☐ Purple – engorged ☐ Yellow – slough ☐ Green – infected ☐ Black – necrotic Surrounding skin ☐ Healthy ☐ Oedematous ☐ Swelling ☐ Macerated ☐ Excoriated ☐ Rash	
Treatment	
Isolation of pathogenic organism/bacteria on wound swab ☐ No ☐ Yes (organism_____)	0 10
Antibiotics given ☐ No ☐ Yes (duration_____days)	0 10
Drainage of fluid / purulent fluid at bedside ☐ Yes ☐ No	0 5
Debridement of wound under general anaesthetic ☐ Yes ☐ No	0 10
Inpatient stay ☐ Not prolonged ☐ Prolonged (>14 days) ☐ Readmitted	0 5

Appendix D. : EQ – 5D- 5L (see attached)

EQ-5D-5L

Health Questionnaire

English version for the UK

Appendix E. POSAS Observer scale (see attached)

POSAS Observer scale

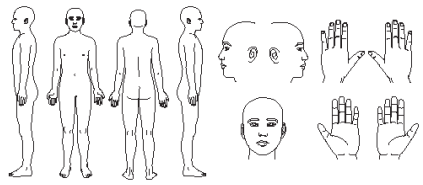
The Patient and Observer Scar Assessment Scale v2.0 / EN

Date of examination: | **Name of patient:**

Observer:

Location: | **Date of birth:**

Research / study: | **Identification number:**



1 = normal skin worst scar imaginable = 10

PARAMETER	1	2	3	4	5	6	7	8	9	10	CATEGORY
VASCULARITY											PALE | PINK | RED | PURPLE | MIX
PIGMENTATION											HYPO | HYPER | MIX
THICKNESS											THICKER | THINNER
RELIEF											MORE | LESS | MIX
PLIABILITY											SUPPLE | STIFF | MIX
SURFACE AREA											EXPANSION | CONTRACTION | MIX
OVERALL OPINION											

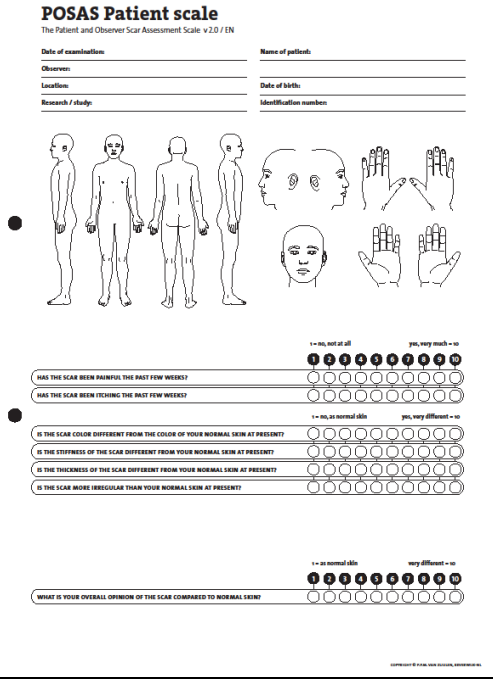
Explanation

The observer scale of the POSAS consists of six items (vascularity, pigmentation, thickness, relief, pliability and surface area). All items are scored on a scale ranging from 1 ('like normal skin') to 10 ('worst scar imaginable'). The sum of the six items results in a total score of the POSAS observer scale. Categories boxes are added for each item. Furthermore, an overall opinion is scored on a scale ranging from 1 to 10. All parameters should preferably be compared to normal skin on a comparable anatomic location.

Explanatory notes on the items:

- **VASCULARITY** Presence of vessels in scar tissue assessed by the amount of redness, tested by the amount of blood return after blanching with a piece of Plexiglas
- **PIGMENTATION** Brownish coloration of the scar by pigment (melanin), apply Plexiglas to the skin with moderate pressure to eliminate the effect of vascularity
- **THICKNESS** Average distance between the subcutical-dermal border and the epidermal surface of the scar
- **RELIEF** The extent to which surface irregularities are present (preferably compared with adjacent normal skin)
- **PLIABILITY** Suppleness of the scar tested by wrinkling the scar between the thumb and index finger
- **SURFACE AREA** Surface area of the scar in relation to the original wound area

Appendix F. POSAS Patient scale (see attached)



POSAS Patient scale

The Patient and Observer Scar Assessment Scale v 2.0 / EN

Date of examination: | Name of patient:

Observer: |

Location: | Date of birth:

Research / study: | Identification number:

1 = no, not at all — yes, very much = 10

HAS THE SCAR BEEN PAINFUL THE PAST FEW WEEKS?

HAS THE SCAR BEEN ITCHING THE PAST FEW WEEKS?

1 = no, as normal skin — yes, very different = 10

IS THE SCAR COLOR DIFFERENT FROM THE COLOR OF YOUR NORMAL SKIN AT PRESENT?

IS THE STIFFNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?

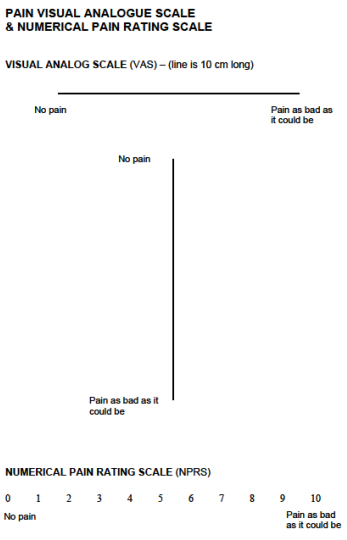
IS THE THICKNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?

IS THE SCAR MORE IRREGULAR THAN YOUR NORMAL SKIN AT PRESENT?

1 = as normal skin — very different = 10

WHAT IS YOUR OVERALL OPINION OF THE SCAR COMPARED TO NORMAL SKIN?

Appendix G. VAS/NRS (see attached)



PAIN VISUAL ANALOGUE SCALE
& NUMERICAL PAIN RATING SCALE

VISUAL ANALOG SCALE (VAS) – (line is 10 cm long)

No pain — Pain as bad as it could be

No pain

Pain as bad as it could be

NUMERICAL PAIN RATING SCALE (NPRS)

0 1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as it could be