**A randomised trial of perioperative use of combination oxidized regenerated cellulose, collagen and silver (Promogran Prisma™) dressing in lower limb minor amputations.**

**Background**

Lower limb amputation is a surgical procedure often necessitated as a means of managing aggressive /refractory chronic infection or irreversible tissue ischemia. These pathologies most frequently occur in the setting of patients with diabetes, peripheral arterial disease or a combination of both.

Minor amputation of the lower limb, defined as being any amputation distal to the metatarsal base, can often progress to major amputation (trans-tibial or more proximal) as a result of failure of wound healing.

Successful wound healing, post minor amputation is dependent on numerous endogenous (nutrition, local perfusion, control of infection) and exogenous factors (infection prevention, moisture balanced wound bed, pressure offloading)1,3. Wound dressings play a key role in controlling many of these exogenous factors1,3. An appropriate wound dressing will promote a moist wound bed, whilst managing excess exudate, bleeding and also contribute to the prevention of infection (both colonisation and external pathogens). A wound dressing should also be designed to be removed atraumatically and easily, in order to minimise pain and further tissue damage at each dressing change.

At Flinders Medical Centre the current wound dressing management of minor lower limb amputations entails intraoperative placement of a calcium alginate dressing (to promote haemostasis) into the wound bed coupled with a silicone adhesive dressing (to facilitate atraumatic dressing removal).

Promogran Prisma ™ is a compound matrix dressing, consisting of 44% oxidised regenerated cellulose, which facilitates wound bed haemostasis5,6, 55% bovine derived collagen, which mitigates excess deleterious proteinases and provides raw protein for tissue matrix regeneration by endogenous fibroblasts and 1% silver which serves as a topical antimicrobial agent1,3,4,7. Due to the nature of its constituents Promogran Prisma ™ promises to be a prospective single-dressing replacement for the aforementioned combination silicone and calcium alginate dressing, whilst adding further advantages such as antimicrobial protection, proteinase mitigation and granulation tissue promotion. Additionally, as this dressing is absorbed by the wound bed, there is no need for active removal of the dressing product, avoiding the need for dressing changes which may traumatise the wound bed.

**Rationale**

We hypothesize that a combination oxidised regenerated cellulose, collagen and silver dressing (Promogran Prisma ™) will be safe to use with an observed reduction in post-operative infection, increased wound healing and decreased frequency of dressing changes when compared with usual standard of care wound dressing practices\* for lower limb minor amputation wounds.

A positive outcome will result in a change of clinical practice.

\*usual standard of care refers to practice which aligns with contemporary wound management practice. See Appendix A for a summary of practice guidelines related to usual standard of care.

**Objectives**

This study aims to answer the following questions:

1. Does Promogran Prsima ™ facilitate improved healing rates in minor amputation wounds when compared with ?
2. Does Promogran Prsima ™ improve wound bed tissue quality in minor amputation wounds when compared with usual standard of care\*?
3. Does Promogran Prsima ™decrease risk of infection in minor amputation wounds?
4. Does Promogran Prsima ™facilitate atraumatic wound dressing changes when compared with current practice?

**Proposed Methods**

1. **Study Design**

Patients undergoing lower limb minor amputation at Flinders Medical Centre for non-salvageable tissue loss, infection or ischemia will be recruited at the time of presentation (either in the out-patient clinic or on admission).

A baseline Wound Ischemia foot Infection (WIfI) score (a validate tool for the assessment of diabetic foot complications)8 will be obtained, to determine healing propensity and to assess extent of underlying peripheral arterial disease / diabetic neuro ischemia8. As part of the WIfI score patients will be required to undergo one or more of the following diagnostic tests:

* Toe pressures assessment
* Ankle-brachial Pressure Index
* Transcutaneous oximetry

These diagnostic tests are performed as part of standard assessment of lower limb perfusion. They are non-invasive tests and are performed by the Dept. of Vascular and Endovascular Surgery Unit . Patients who have recently undergone one or more of these tests (within 4 weeks of lower limb minor amputation surgery) will not be required to repeat these tests.

Patients will be randomised using a pre-randomised secret envelope system containing random assignment to either control or trial group, available at the time of lower limb minor amputation:

1. A control group, who will receive the usual standard care for post-operative minor amputation wound management. The usual standard of care at our institution consists of a calcium alginate dressing and a silicone adhesive dressing placed into the wound bed and covered with absorbent secondary dressings secured with crepe bandage. This dressing will be removed at the 48 hour mark unless otherwise indicated. The patient will then receive ongoing wound management as determined by the vascular surgery unit clinical team, however the patient is not to receive Promogran Prisma ™ as a primary dressing at any point during the 12 week follow-up period.
2. A trial group who will receive Promogran Prisma ™ as primary dressing, placed into the wound bed post completion of minor amputation, The Promogran Prisma ™ will be covered with absorbent secondary dressings and secured with crepe bandage. The dressing will be reviewed at the 48 hour mark unless otherwise indicated. The patient will continue to use Promogran Prisma ™ as the primary wound dressing and will remain the only variable to standard minor amputation post-operative wound management for a period of 12 weeks. This group will be used to assess the effect of Promogran Prisma™ as a primary wound dressing for minor amputations.
3. Standard procedures for histology and microbiological sampling will be adhered to for all cases.
4. Blinding is not possible in this research project due to distinct product variances between Promogran Prisma™ (trial) and dressings used in usual standard of care (control).

Clinical post-operative management will be standard for both groups, with a wound bed review at ≤48 hours post initial procedure and then ongoing clinical review and management as clinically indicated.

Frequency of dressing changes for either control or Promogran Prisma ™ will be set by the supervising clinical team, as clinically indicated, however frequency of dressing changes must meet a minimum review period of 72 hours for both trial and control groups.

**Outcomes**

The primary outcome measure is percentage of wounds that achieve complete healing within a 12 week period, as outlined below:

1. Proportion of patients with 100% wound healing defined as: 100% wound bed epithelialisation prior to or by the end of the trial timeframe (12 weeks). Assessments of wound healing progress will be made at each outpatient clinic encounter. A senior vascular nursing clinician or consultant surgeon will assess the wound and designate the wound to either be ‘completely healed’ as per above definition or ‘healing incomplete’ at time of each assessment.

Secondary outcome measures will provide additional data points to ascertain correlation between wound healing time frames and type of wound dressing product used:

1. Time to complete wound epithelialisation – defined as number of days from date of minor lower limb amputation surgery to date of 100% wound bed epithelialisation.
2. Rate of wound healing, to be ascertained through absolute (cm2) and relative (%) wound surface area and tissue volume reduction, this will include clinical photography of the wound bed:
	1. Wound planimetry measurements, calculation of wound surface area facilitated through tracing of wound margins using a sterile transparent film and use of the Smith and Nephew Visitrak wound planimetry device to calculate wound surface area measurements in cm2
	2. Measurements to be taken at 48 +/- 12 hours, 10 days (+/- 3 days), 4 weeks(+/- 5 days), 8 weeks (+/- 5 days) and 12 weeks (+/- 5 days) post minor amputation surgery post minor amputation.
	3. A wound surface area reduction of >50% at 4 weeks of treatment has been validated as a good prognostic indicator of wound healing.15
3. Wound bed tissue quality, to be facilitated through use of the Wound Bed Score2 – a validated tool to objectively quantify quality of wound bed tissue, assessment to be performed at 48 +/- 12 hours, 2 weeks (+/- 3 days), 4 weeks(+/- 5 days), 8 weeks (+/- 5 days) and 12 weeks (+/- 5 days) post minor amputation surgery.
4. Decrease in pain related to wound dressing change procedures. Pain will be assessed before and after dressing change procedure using a visual pain scale (allows for verbal an non-verbal assessment of pain).
5. Decrease in infection rates to be observed in the Promogran Prisma™ group – wounds will be assessed and scored according to the definitions outlined in the Infectious Diseases Society of America and International Working Group on the Diabetic Foot Classifications of Diabetic Foot Infection – Clinical Manifestations of Infection (a validated tool)10.
6. Decrease in total number of dressing changes required - Total number of dressing changes from day of initial amputation surgery will be recorded.
7. Revascularisation post minor lower limb amputation – defined as any patient requiring either a peripheral angiogram procedure or arterial bypass procedure to facilitate revascularisation of the lower limb on which amputation surgery has occurred. Revascularisation of lower limb arteries of a limb which has undergone minor amputation is an endpoint for patient participation in the study as changes in peripheral perfusion present a confounder to impact of dressing product on tissue regeneration.
8. Major limb amputation, defined as amputation of at trans-tibial or proximal, of the limb which has undergone minor amputation is an end point for patient participation in the study.

All scoring methods, assessment tools and wound measurement processes are non-invasive.

Other trial participant data to be collected (within 48 hours of being enrolled in the trial):

* Age, gender
* Height, weight and BMI calculation
* Relevant comorbidities – History of: diabetes (type, duration from initial diagnosis), peripheral arterial disease, venous insufficiency disease and ischemic heart disease.

The above metrics are collected as part of standard demographic and patient assessment data. Informed consent for access to this information will be obtained prior to patient enrolment to the study.

1. **Study Duration**

15 months (12 months of recruitment and 12 weeks of follow-up).

1. **Participant Selection**

All patients admitted to the Flinders Medical Centre Vascular Unit who are to undergo minor amputation of the foot, defined as being any amputation distal to metatarsal (includes trans metatarsal amputations), will be eligible to participate in the trial. Participants will be identified through treating vascular surgeons who will notify the study coordinator regarding plans for minor amputation surgery. The Study Coordinator is separate from the clinical decision process to proceed to amputation and is therefore considered separate from the dependant relationship that exists between Vascular Surgeon and participant.

1. **Inclusion Criteria**

All patients undergoing minor amputation of the foot (single or multiple digits, to base of metatarsal as maximum depth debrided / amputated) at Flinders Medical Centre, where the surgical site has been left open to heal via secondary intention.

1. **Exclusion Criteria**
2. Patients who live interstate, rural or remote or who are not able to attend the scheduled appointed review time frames.
3. Patients under 18 years of age.
4. Patients who are unable to give informed consent due to language difficulties or physical/mental incapacity.
5. A minor amputation where the operative wound bed has been closed using primary closure methods (suture, staples).
6. Patients with known hypersensitivity to any components of Promogran Prisma™ - oxidised regenerated cellulose, collagen and silver.
7. **Withdrawal Criteria**

Participants will be informed that they may withdraw from the study at any time (as outlined in the PISCF), without the need to specify a reason for doing so, and that this will not result in any change to their care or treatment.

1. **Consent**

Patients identified as prospective participants by the treating surgeon will be screened by the treating surgeon for suitability (inclusion/exclusion) prior to referral to the study coordinator for obtainment of consent.

Written consent in the form of a signed and dated consent form will be facilitated by the study coordinator, who will provide the participant with information about the trial, answer any questions the patient may have about the trial and provide the participant with a physical copy of the PCIF.

A delayed decision to participate in the trial will not influence or delay a decision to progress to limb saving surgery when deemed clinically necessary by the treating surgeon. In these instances the patient will be deemed ineligible for participation in the trial. Consent to participate in this trial can only be obtained prior to performance of the lower limb minor amputation procedure.

1. **Safety profile of Promogran Prisma™**

PROMOGRAN PRISMA has been tested and risk assessed in accordance with ISO 10993-1 with no issues identified. For the period July 2014 to December 2018 the company has reported sensitivity reaction or pain associated with use at an incidence rate of 0.7 per million items sold.

1. **Sample Size calculation:**

A multicentre RCT comparing use of a protease mitigating dressing16 (Collagen/oxidised regenerated cellulose/silver) versus care using control wound management products in a diabetic foot ulcer cohort demonstrated a 26% percentage point increase (p=0.035) in wound area reduction rates when compared with the control group. This study recruited a total of 39 patients, (24 trial [79% >50% wound surface area reduction]; 14 control [43% wound surface area reduction].

Utilising the results from the above trial as anticipated incidence for the outcomes of our trial a power calculation using clincalc.com has outlined a sample size of 56 patients (28 each arm) to achieve 80% power at 0.05 significance level.

Flinders Medical Centre performed a total of 117 minor amputations in 2017, hence the study enrolment duration has been set as being 12 months, to allow enough time for single centre enrolment of the nominated sample size and to also allow for an approximate 15% drop out rate and 75% eligibility of our minor amputation cases.

1. **Data Collection/Gathering and Management**

All study participants are required to have photographs and measurements taken of their minor amputation wounds at scheduled intervals (48 hours, 2,4, 8 and 12 weeks post surgery) . These details will be stored on a shared access computer which is property of the South Australian government (SA Health). Access to this data and images will only be available to clinicians directly involved in this research project, the study coordinator and the Principal Investigator. This data will be stored on a secure SA Health server. Data collected will be stored on a secure server for a total of 15 years, from date of research project completion before being deleted.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that participants will not be identified, except with participant permission. Photographs containing patient details will be de-identified prior to publication.

Participants will be assigned subject codes which will serve to de-identify subject information stored in the trial database which will house the details data points outlined in the Outcomes section of this project plan. A separate reference file will provide the means to decode the participants subject code to allow for identification when necessitated (clinical reasons).

Information pertaining to clinical follow-up visits will be entered in the patients’ health record (Flinders Medical Centre case notes) as part of the usual standard of care.

1. **Budget**

Budget for this project is expected to be conducted using in-kind support and operating budget.

The wound dressing proposed for the trial – Promogran Prisma™ is currently a tender item on SA Health Wound Dressings and Bandages tender and is approved for use at all SA Health sites. Control groups will be utilising ‘usual standard of care’ which incorporates a range of dressing products (see Appendix A) which are currently used for treatment of post operative wounds. There is no cost variance with Promogran Prisma™ when compared with ‘usual standard of care’ dressing regimes.

Clinician support for this role will be provided as in-kind support and facilitated within normal business hours and within existing roles. It is a predicted a total of 0.05 Consultant Surgeon FTE (less than one day a month) will be required to facilitate recruitment and clinical follow-up of participants and can be argued to be part of their core work role.

Data collection and analysis will be facilitated by our Level 2 Clinical Research Nurse, who is currently funded by SPF funds and therefore has no impact on operational budget.

Study coordination will be provided through in-kind support of the Vascular Surgery Nurse Practitioner role which will absorbed within their current role. An estimated 0.1 FTE of Vascular Nurse Practitioner time will be required – the Nurse Practitioner role currently has 0.4 FTE of non-clinical/research time allocated to the role.

There will be a small amount of photocopying/printing required for the data template, consent forms and PCIF. This is estimated at being: $40-100 (400 to 1000 pages of black and white printing at $0.10 per page). This amount is to be accommodated by the organisational budget.

Estimated total cost to Vascular Surgery operational budget - $100.00 in printing.

1. **Randomisation Method**

Sequence generation will be facilitated using [www.sealedenvelope.com](http://www.sealedenvelope.com), using the following parameters: Two treatment groups assigned as "Promogran" and "Standard"; assigned a black size of 2 and a list length of 56. The list will be generated using the unique randomisation code, thus randomisation will be blinded.

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**Appendix A**

For the purpose of this study all study participants will be subject to the following wound management guidelines. These guidelines have been informed by wound management literature11,12 and clinical consensus and local health institution policy. For the purpose of this study these guidelines form the usual standard of care for wound management.

**Wound Assessment**

Evaluation of the wound bed should include assessment of wound bed tissue quality, presence of infection or inflammation, wound exudate volume, nature and moisture balance and status of wound edge. Wound assessment is to be conducted by a suitably qualified professional and assessment findings inform the development of the wound dressing care plan.13,14

**Wound Bed Preparation**

Wound bed preparation is a core principle of contemporary wound management and focuses on clinician based interventions to facilitate positioning of a wound bed to be optimal for wound healing. Core to this principle are the following goals:

* A wound bed which contains viable granulating tissue
* A wound bed which is free from slough, necrotic or non-viable tissue
* Wound edges which are epithelializing and advancing
* Wound edges which are not impeded by debris, callus or retained dressing materials

There are a variety of methods employed by medical, nursing and allied health professionals to facilitate wound healing. Regular cleaning of a wound bed using sterile gauze and normal saline, and suitable mechanical pressure to assist in the removal of any non-viable tissue is advised on each dressing change. Wound bed preparation practice is considered part of the ‘usual standard of care’ for wound management practice.

**Wound Dressing Care Plan**

The wound dressing care plan is a detailed regime outlining the procedure for dressing of a wound, in this instance a wound related to a minor lower limb amputation. The dressing care plan typically outlines the process of wound bed preparation (cleaning, debridement or application of antiseptic solutions); the dressing products to be applied to the wound bed and the duration of wear / interval between dressing changes. 13.14

The wound dressing regime consists of primary (dressings in contact with the wound bed) and secondary dressings (supportive dressings which facilitate exudate management and/or securing of the products to the patients skin). For the purpose of this study the trial group will always use Promogran Prisma™ as the primary dressing in combination with a secondary dressing selected by the treating clinician. The control group will utilise a primary and secondary dressing selected from the lists outlined below.

For the purpose of this study the following wound dressing products will be considered suitable for use in the control group in context of establishing a usual standard of wound management.

**Topical Negative Pressure Wound Therapy** – a vacuum assisted wound dressing device which facilitates tissue granulation, wound tension support, exudate management and occlusive dressing. These devices are utilised for rapid granulation of large tissue deficits. They may be utilising in both inpatient and outpatient setting. This dressing product is suitable for use in both the trial arm and the control arm. If this dressing is used in the trial arm it will be placed over the Promogram Prisma™ which will be placed in the wound bed as a primary dressing. These dressings are placed in direct contact with the wound bed.

**Topical Antimicrobial dressings (primary)**

There are a wide range of topical antimicrobial dressing products on the market. For the purpose of this study we will limit the use of these dressing products to a common cluster of products which have established use within the South Australia health service and community nursing services. The following list outlines topical antimicrobial dressing products suitable for use in the control arm of this trial. These dressings are placed in direct contact with the wound bed.

It should be noted that Promogran Prisma™ has a silver component and therefore is considered an antimicrobial/anti-inflammatory topical wound dressing product.

* Silver containing hydrofibre
* Silver containing mesh dressings
* Silver containing polyurethane foam
* Silver containing silicone foams
* Povidone Iodine impregnated gauze
* Cadaxomer Iodine paste
* Cadaxomer iodine sheet
* Polyhexamethylene Biguanide Foam
* Polyhexamethylene Biguanide Gauze
* Polyhexamethylene Biguanide Gel
* Sterile honey and alginate fibre dressings

**Primary Dressings**

The following list outlines non-antimicrobial primary dressing approved for use in the control arm of this trial. These dressings are placed in direct contact with the wound bed.

* Amorphous hydrogel
* Amorphous hydrogel and gauze compound
* Saline soaked gauze
* Polyurethane foams

**Absorbent Secondary Dressings**

Absorbent secondary dressings are utilised in combination with primary dressings to manage exudate. These dressing are not typically placed in direct contact with the wound bed, but are placed over/on top of the primary dressing.

These dressings are approved for use in this study in either the trial or control arm. Secondary dressing choice is based on exudate volume and will be determined by an appropriate qualified health care professional.

* Superabsorbent polymer dressings
* Combine/cotton absorbent dressings
* High absorbent dressing with fluid repellent backing
* Gauze
* Polyurethane foams

**Adhesive dressings**

Adhesive dressings are utilised as either an ‘all in one’ solution for securing dressing products, providing a primary contact layer and secondary absorbent layer or they are utilised to secure primary and secondary dressings described in the above categories. For the purpose of this study the following adhesive dressings are suitable for use in both the trial and control arm of the study.

* Hypoallergenic paper adhesives
* Paper tape adhesives
* Silicone adhesive foams
* Silicone adhesive matrices

Appendix B

Clinical Manifestations of Infection – an excerpt from the Infectious Disease Society of America and International Working Group on the Diabetic Foot Classifications of Diabetic Foot Infection (2012)

