Study Protocol: PICASSo Trial

Prophylactic InCisional Antibiotics in Skin Surgery (PICASSo trial)

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TABLE OF CONTENTS:

PICASSo: PROJECT SUMMARY

Title	Study Protocol: PICASSo Trial Prophylactic InCisional Antibiotics in Skin Surgery Trial registration number: ACTRN12616000364471
Methodology	Prospective, randomized, double-blind, placebo-controlled study Superiority analysis of interventions versus standard of care (control)
Study Duration	6.5 months
Study Center	Middlemore Clinical Trials Unit. Counties Manukau District Health Board (CMDHB) Middlemore Hospital 100 Hospital Road Papatoetoe, Auckland 1640 New Zealand
Objectives	Primary Objective: to evaluate the efficacy and safety of a single dose of preoperative locally-infiltrated incisional antibiotics for decreasing the incidence of Surgical Site Infections (SSIs) in patients undergoing skin surgery Secondary Objectives: Evaluate associated risk factors for SSI in skin surgery; evalute organisms cultured in SSIs, and systemic antibiotics prescribed for managing SSIs in skin surgery
Number of Subjects	At least 987 lesions (or 987 patients assuming 1 lesion per patient, and 100% follow up rate) based on pre-recruitment power analysis, randomized into three arms: two treatment arms and control. See “Statistical Analysis Plan: PICASSo Trial” for details of power analysis
Diagnosis and Main Inclusion Criteria	Inclusion Criteria: All patients undergoing skin cancer surgery at the Auckland Regional Platic Surgery Unit under local anesthetic over the 6-month recruitment period will be eligible. Exclusion criteria: Any patients allergic to both penicillin and clindamycin preoperative systemic intake of any antibiotic within 7 days of skin surgery or inability to return for face-to-face postoperative wound assessment. Patients can be enrolled and randomized more than once if they

	underwent additional procedures within the study period, assuming all eligibility criteria were still met.
Study Product, Dose, Route, Regimen	Control Group: 1. buffered local anesthetic alone (1% lidocaine plus adrenaline 1:100,000 standard solution buffered 1:10 with 8.4% sodium bicarbonate) Treatment Groups: 1. buffered local anesthetic + micro-dosed flucloxacillin (500 µg/cc), or 2. buffered local anesthetic + micro-dosed clindamycin (500 µg/cc). Hypodermic infliltration (standard local anaesthetic/field anaesthetic technique) Surgical excision, reconstruction, and perioperative management will proceed as per the usual standard of care, and all interventions and assessments will be performed by investigators unaware of treatment allocation. See “Standard Operating Procedure” below for protocol workflow details
Statistical Methodology	Primary outcome measure is Surgical Site Infection (SSI) as defined by maximal standardized Post-Operative Wound Infection (POWI) score recorded at any follow up visit, per lesion, with a value greater than or equal to 5 [scale, 0-7], by arm. See “Statistical Analysis Plan: PICASSo Trial” for details of Statistical Methodology

Objectives:

The primary objective of the Prophylactic InCisional Antibiotics in Skin cancer Surgery (PICASSo) trial is to evaluate the efficacy and safety of a single dose of preoperative locally infiltrated incisional antibiotics for decreasing the incidence of SSIs in patients undergoing skin cancer surgery.

The overarching goal is to lead the way in delivering high quality economical skin cancer treatment, while filling a void for evidence-based guidelines in skin cancer surgery that would be applicable worldwide

Background:

Skin cancer is by far the most common cancer worldwide. It also represents one of the most expensive cancers. Surgical site infections (SSIs) represent one of the most significant, potentially avoidable factors that negatively impact on skin

cancer treatment costs, patient experience and outcomes.

The Auckland Regional Skin Cancer Treatment Centre at Counties Manukau District Health Board (CMDHB) is one of the busiest skin cancer treatment centres in New Zealand, receiving >2000 patient referrals per year. The rate of SSI at this centre in a recent evaluation fell between 3.5% and 14.3%, and published rates of SSI after cutaneous surgery internationally have been reported to be 2.3-4.3%.

While the routine adoption of evidence-based antibiotic prophylaxis has been associated with substantial decrease in the rate of SSIs in other surgical streams, there is a general lack of high-quality studies evaluating the role of prophylactic antibiotics in skin cancer surgery, and no evidence-based guidelines directly applicable to skin cancer surgery exist, either regionally or globally.

Furthermore, there is an increasingly urgent need to develop antimicrobial prophylaxis approaches that incorporate good antibiotic stewardship and reduce the devastating potentiation of antibiotic resistance.

Duration of Study:

The study is estimated to complete adequate recruitment to meet power analysis within 3 months from study initiation; however, recruitment will remain open at least 6 months from study initiation to ensure study goals are met. Assessment will continue for at least 3 weeks following final recruitment but will continue as long as required in parallel with management of any SSIs encountered to point of SSI resolution. The duration of this study for each subject will be at least 3 weeks spanning from date of recruitment/randomization to planned follow up, or for as long as required to manage any SSI's encountered to point of SSI resolution.

Methods:

Study Design:

This is a prospective, randomized, double-blind, placebo-controlled study

Patient Population:

All patients undergoing skin cancer surgery at the Auckland Regional Platic Surgery Unit under local anesthetic over the 6-month recruitment period will be eligible.

Exclusion criteria: Any patients allergic to both penicillin and clindamycin, preoperative systemic intake of any antibiotic within 7 days of skin surgery, or inability to return for face-to-face postoperative wound assessment.

Patients can be enrolled and randomized more than once if they underwent additional procedures within the study period, assuming all eligibility criteria were still met.

Consent:

All qualifying patients will be invited to participate in the study and informed consent will be obtained preoperatively in conjunction with routine surgical informed consent. The methodology has been approved by the Central Health and Disability Ethics Committee (HDEC Full Review Pathway; ref 15/CEN/260) (see appendix below).

Randomization:

Randomizations will be performed among arms 1:1:1 using a blinded schedule generating a randomization number, with random block sizes. Patients randomized to the flucloxacillin arm with a penicillin allergy will be automatically re-allocated to the clindamycin arm (second line antibiotic, also blinded, assuming no clindamycin allergy), and patients randomized to clindamycin who with a clindamycin allergy will be automatically re-allocated to control arm.

Interventions:

Participants will receive blinded incision site injection of buffered local anesthetic alone (1% lidocaine plus adrenaline 1:100,000 standard solution buffered 1:10 with 8.4% sodium bicarbonate; “control”), buffered local anesthetic + micro-dosed flucloxacillin (500 µg/cc), or buffered local anesthetic + micro-dosed clindamycin (500 µg/cc) according to randomized allocation as outlined above.

Surgical excision, reconstruction, and perioperative management will proceed as per the usual standard of care, and all interventions and assessments will be performed by investigators unaware of treatment allocation.

Lesions will be infiltrated using a pre-filled infiltration syringe based on randomization number and corresponding to the allocated treatment group that had been prepared by a trial pharmacist (Baxter Pharmaceuticals) in 10cc aliquots. To promote blinding integrity, syringes will be labelled in a random order within each batch. Syringes will be stored at 4ºC, protected from light, and replaced with a fresh batch every 48 hours. Patients and all members of the surgical and follow-up teams will remain blinded to allocation until study conclusion. If more than one syringe is required (e.g. large infiltration area and/or multiple sites), the original allocation arm will be maintained for that patient-presentation. Participants enrolled more than once will be independently randomized at each presentation. Any deviations to treatment received compared with protocol will be recorded.

Surgical excision, wound closure/reconstruction, and postoperative management will be performed according to standard of care. Patients will be monitored for adverse reactions perioperatively and questioned about sensitivity reactions elicited at each follow-up visit. Safety will be monitored by an independent data monitoring committee throughout the trial.

Assessments:

All assessments will be performed by clinical staff blinded to treatment group allocation.

All participants will undergo standardized postoperative assessment by a

consistent trial nursing team between 7 and 21 days postoperatively. Additional assessments will also be also performed opportunistically during any further encounters (for example in case of wound healing concerns and/or surgical site infections requiring further management) as required.

Each assessment will include a patient questionnaire eliciting any side effects experienced, adverse events, and/or antibiotics prescribed for any reason since the time of operation and/or last assessment. A standardized wound assessment will be performed for each operative site using a previously validated Post-Operative Wound Infection (POWI) scoring system [scale, 0-7, with 0 reflecting no signs or symptoms of infection, and 7 reflecting obvious signs and symptoms of severe infection]. When more than one post-operative assessment is made, the highest POWI score recorded for each lesion will be used for analysis. Additional data recorded based on surgical type will including length of closure and any dehiscence (for wounds closed directly), percent skin graft take (grafted wounds), and area of local tissue rearrangement (skin flaps).

Standardized POWI score is defined as follows:

Score	Condition
0	Normal healing
1	Normal healing but with one of the following signs of infection: erythema, edema, or increased pain
2	Normal healing but with two of the following signs of infection: erythema, edema, or increased pain
3	Normal healing but with three of the following signs of infection: erythema, edema, and increased pain
4	Hemoserous discharge combined with two of the following: erythema, edema, or increased pain
5	Pus combined with one of the following: erythema, edema, or increased pain; or hemoserous discharge combined with all three of the following: erythema, edema, and increased pain
6	Pus combined with two of the following: erythema, edema, or increased pain
7	Pus combined with all three of the following: erythema, discharge and increased pain

For wounds with overt signs of infection (e.g. skin breakdown or skin graft loss with drainage), culture swabs will be obtained for microbiology analysis (as per clinical routine).

Patient-specific factors will be recorded for each participant including immunosuppression; glucose intolerance; history of prior Surgical Site Infection (SSI); smoking status; and, for extremity wound sites, peripheral edema score, presence of venous insufficiency and peripheral pulse palpability. In any case of overt infection, culture swabs will be obtained for microbiological analysis and to guide tailored antibiotic treatment.

Unscheduled Visits:

The same assessments will be opportunistically performed if any subject presents to the postoperative clinic for any reason at any time point other than for the scheduled standardized postoperative assessment as detailed above. These assessments will include: patient questionnaire, assessment for any adverse events, assessment for any complications of treatments, documentation of any antibiotics prescribed, and wound assessment according to standardized POWI scoring system as shown above.

Responsiveness to Maaori (New Zealand Indigenous Minority):

Maaori consultation and approval were obtained as part of the HDEC Central Health and Disability Ethics Committee Full Review pathway. Maaori are affected by skin cancer, although at a lower rate than the NZ European population. However, Maaori often present at a later stage and have a worse prognosis. This study aims to improve outcomes for all patients undergoing skin cancer surgery. However, the centre at which the trial will be conducted includes the highest proportion of Maaori and Pacific Island peoples of any District Health Board in New Zealand. Therefore, Maaori patients will be included in the study and the data obtained will be relevant to Maaori.

Ethics:

The PICASSo study including protocol outlined herein has obtained full ethics approval through the New Zealand Central Health and Disability Ethics Committee (HDEC Full Review Pathway; ref 15/CEN/260).

Evidence of HDEC certification provided as a supplement to this document.

Adverse Reactions:

To reduce the risk of adverse hypersensitivity reactions, all study patients are screened for prior adverse events before medication administration, with further validation by the nursing team prior to any intervention. Patients with known or documented sensitivity to penicillin or clindamycin will be excluded from the respective intervention arms but remain included for alternative intervention/control arms according to study protocol.

Patients will be monitored in the presence of doctor for hypersensitivity during infiltration and surgery, and for at least 30 minutes postoperatively in recovery as per clinical routine at the skin surgery unit. This initial part of the study takes place on a hospital campus (Middlemore), with easy access to facilities including an emergency room, ICU and inpatient care capability. Contact details for after-hours advice and no-cost 24 hour/7 day per week access to emergency room assessment will be ensured for all study participants through Middlemore Hospital (CMDHB).

In case of unanticipated major hypersensitivity reaction (anaphylaxis), staff are trained to recognize and treat this condition with cardiopulmonary monitoring equipment and adrenaline on site. Minor hypersensitivity reactions could include localized skin reactions including rash, oedema, and pruritus. These reactions usually self-resolve with discontinuation of localized antibiotic administration, and are well controlled with conservative measures such as cold compresses, antihistamines, and low-potency topical corticosteroids. All adverse events are recorded, and will be factored into outcome analyses.

Reasons for Withdrawal or Termination:

A participant may be discontinued from the study at any time if the participant or investigator feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study discontinuation:

1. screening failure
2. participant withdrawal of consent
3. adverse event that in the opinion of the investigator would be in the best interest of the participant to discontinue study participation
4. lost to follow-up
5. participant death

Handling of Participant Withdrawals or Termination

Although participants may withdraw from the study at any time and for any reason, (or may be withdrawn at the Investigator's discretion), participant withdrawal will be avoided as much as reasonably possible. In any case, appropriate clinical follow-up for treatment recovery will be continued. Participants who prematurely discontinue will not be replaced. For participants lost to follow-up, data collection will be retained up to the last visit/assessment performed.

Data Monitoring:

The Principal Investigator will be responsible to ensure the study is conducted in accordance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and that the data recorded is valid.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial complies with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Data Handling and Record Keeping:

A custom clinical trial database that has been developed by a CMDHB-vetted healthcare software solution company (MedSyn Software, Auckland; see Appendix below for representative screenshot). The database links to CMDHB's existing medical records system to ensure error-free extraction of patient demographics (e.g. age, gender, ethnicity). Other study parameters, including injectable solution code,

POWI scores, surgical site, procedure type, and SSI-associated factors will be recorded in the database prospectively.

The collection of personal patient information will be limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

Only study personnel will collect and analyze data. Hard copy documents will be retained for the duration of the study until data entry. All hard copy documents will be kept in a locked cabinet in the principal investigator's office. Electronic data entry will be completed in the secure PICASSo trial database. All hard copy documents will be shredded within five years after completion of the study.

Database data will be exported into Excel and statistical analysis software (password protected), which will then be used for data analysis. Only de-identified data will be used for data analysis.

All patient data will be handled using best practice guidelines in terms of maintaining patient confidentiality, including data encryption with controlled access.

Detailed Protocol Workflow

This following information outlines the standard workflow of the PICASSo clinical trial.

Prior to arrival:

- Patients are accepted to the Middlemore 'See and Treat' skin cancer treatment Unit (MSTU) by General Practitioners and specialists for evaluation and management of skin lesions. Skin lesions include, but not limited to, squamous cell carcinomas, basal cell carcinomas, and melanomas.
- Referrals are vetted and triaged by specialist plastic surgeons prior to patient arrival based on photographic and/or histological diagnoses.

Day of surgery/check in area:

PICASSo database opened on computer in each procedure room at the start of the day by staff. The relevant patient files for each surgical case are available and prepared in order of operating list in MSTU reception.

- Patients arrive on the day of their surgery and are checked in at the front desk by receptionist and nursing staff
    - PICASSo posters are displayed in the waiting room to provide information and generate interest
- Patients are provided with PICASSo information sheet and consent form (see appendix), and asked by nursing staff whether they would like to take part in the PICASSo trial. Further questions will be answered during the pre-surgery consultation by the clinical specialist surgeon, clinical nurse, and/or a member of the research team.

- MSTU nursing staff are knowledgeable about the purpose of the project, exclusion criteria, and follow-up arrangements, so that they can answer some questions
- Exclusion criteria:
  - history of allergic reaction to both flucloxacillin and clindamycin, preoperative systemic administration of any antibiotic within 1 week of surgery, and inability to return for follow up evaluation

- The provided information sheet and consent forms are provided to patients which outlines:
  - Name and purpose of project
  - Safety and details of ethical approval
  - Results of previous pilot trial
  - Commitment required from them (eg: required follow-up)
  - Exclusion criteria
  - Contact information of principal investigator (PI)

- Patients are encouraged to contact PI at any time for any questions, concerns or adverse events
- Patient will be re-assessed for whether they pass the inclusion/exclusion criteria by the present research nursing staff and/or senior specialist surgeon ("consultant") and/or junior trainee surgeon ("registrar")

<u>Consultant review pre-surgery (clinic room):</u>

All patients reviewed and consented by consultants and/or registrars a pre-procedure appointment

- PICASSo trial is discussed in further detail and informed consent is gained here
  - If a patient gives informed consent to partake in PICASSo, a signed consent form is placed in the notes to alert the operating team in the procedure room

Once review is completed, patients change into gowns for surgery. They return to waiting room to await procedure.

For each case, the operating surgeon receives the patient file with the signed or unsigned PICASSo consent form.

- All patient details are loaded into the PICASSo database (by either surgeon and/or Nursing staff).
  - For excluded patients, reasons for non-participation are collected in database (Eg: antibiotics within the past week, patient not willing to consent to study)

- PICASSo included patients: are randomized to receiving local anesthetic by database software running blinded randomization schedule to either control or intervention arms [local anaesthetic with 500mcg/mL flucloxacillin, local anaesthetic with 500mcg/mL clindamycin, or the control (local anesthetic alone)] as per the randomization protocol. These solutions are numbered by the

Middlemore Hospital clinical trial pharmacy beforehand. Patient and all members of the operating team are blinded as to which arm is being employed.

- For patients who have consented and randomized, the database informs the surgical staff of which pre-loaded syringe to collect. All syringes appear outwardly identical except for number. Staff retrieves the syringe and hand to operating surgeon for each individual patient, with syringe identity confirmed at time of handover.
- In the event that a treatment/control arm has been exhausted from the on-site supply, the PICASSO database will create an automatic pop-up box, and recruitment will cease for the remainder of the operating day until another supply is obtained.

Surgery (procedure room):

- The patient arrives to the Procedure Room and is positioned by the nursing staff on the operating table as lesions in different locations require different positioning e.g. patient lying on their side or on their back
- Operating surgeon infiltrates (injects) the solution from the syringe randomized into operative site per standard of care.
    - Local anaesthetic numbs the lesion, ready for surgical removal
    - The operating surgeon either verbally informs the circulating nurse how much solution was injected, or manually enters this value into the database, as well as surgical site details such as anatomic location.
- In the situation where more solution is needed, (e.g. multiple lesions requiring greater volume of solution than anticipated) this is entered into the database and a second syringe is allocated
    - staff retrieves second syringe from the supply and verify at handover as above.
- Patient prepped for surgery. Operating surgeon +/- scrub nurse scrub and are now sterile

Surgery commences:

- If more solution is needed than anticipated at this point (for example, if local anaesthetic effects have worn off) the remaining contents of the original syringe are emptied into a sterile container by the circulating nurse, which the operating surgeon then transfers to a sterile syringe to maintain procedural sterility.
    - If the original syringe is completely used, another one can be allocated through the database and the same steps as above are used to maintain procedural sterility. The database automatically maintains consistent randomization arm throughout surgical visit in blinded fashion.
- Once surgery is completed, operating surgeon un-scrubs
    - Syringes are discarded as per standard Infectious Disease protocol in appropriate sharps containers

- Multiple lesions and details are recorded individually into the PICASSo database
- For full thickness skin graft procedures, both primary lesion site and graft donor site details are recorded.
- Entry on database record is saved and closed
- Database is backed up daily by study team.

Post-Procedure:

- The patient returns to a waiting area for a period of observation after their surgery.
- In the event of a suspected adverse reaction, trained doctors and nurses assess and manage as clinically indicated . All adverse events are recorded in the database. All information relevant to event entered in database (free-text box) Additionally, all events aligned to standardized Common Terminology Criteria for Adverse Events (CTCAE) criteria codes by research staff at study conclusion.
- An Electronic Discharge Summary (EDS) is completed by treating staff.
  - Follow-up box on EDS marked to indicate 'PICASSo Research Nurse Clinic'
- Patient is discharged home

Outpatient Follow up (Manukau Super Clinic)

- All patient reviews performed by one of two dedicated subspecialty trained plastic research nurses at a single dedicated outpatient clinic (the "Manukau Super Clinic") at all time points.
  - If one research nurse is unavailable, the other will be called in to perform assessment
  - If both nurses unavailable, one of the trained blinded research team (eg PI or RMO study coordinators) will perform assessment
- Patients verbally asked all questions of "Health Intake Questionnaire" at each initial visit by research nurse and this information recorded
- Patients additionally verbally asked to report on the following at ALL visits by research nurse and this information recorded
  - Have you had any wound problems, any interventions, and/or any antibiotics since last encounter?
- Surgical sites are reviewed routinely within 5-21 post-operatively, and additionally at any other clinic visits if concerns for SSI identified at initial assessment or any time thereafter. Wounds also reviewed at any incidental visits to the plastic surgery in the research outpatient module. All data recorded in PICASSo database prospectively at each time point

- Wound evaluation includes suture removal (if indicated), dressing changes (if indicated), wound checks of all operative sites.
- In patients with multiple surgical sites, each wound will be assessed separately.

- All Wounds assessed and assigned a Post-Operative Wound Infection (POWI) score according to standardized scoring system
  - For full thickness skin grafts, the donor site is also assessed.
- Digital photographs are taken of the wound at each visit
- Patients are given research nurse contact details and encouraged to contact at any time between visits for any concerns or adverse events

Statistics

The following provides information on statistical analysis for the PICASSo study. See separate "PICASSo statistical Analysis Plan" for further details.

Sample Size:

A pre-recruitment power analysis calculation was performed based on a retrospective analysis of Surgical Site Infections encountered in skin surgery undertaken at the Auckland Regional Plastic Surgery Unit (same unit as current study) over a 6-month period at the same as follows: In a retrospective analysis, ICD10 codes were used to identify all outpatient skin excisions performed at the unit over 6 months in 2015. Medical records were individually reviewed, and data obtained on patient demographics, comorbidities, surgical type, and utilization of perioperative antibiotics.

A total of 2,088 lesions were excised from 938 patients in 1053 encounters over the 6-month evaluation period. Seven patients (0.7%) were readmitted for wound infection within 28 days of excision, clinic letters noted infection in 56 patients (5.2%), while 143 (13.4%) were prescribed antibiotics in the community within 21 days after surgery. It was concluded that the actual rate of SSI was between 3.5% and 14.3% based on these direct versus direct + indirect indicators, respectively. These rates were averaged to estimate the expected SSI rate of 7%.

The anticipated SSI rate in the treatment group was then estimated to be 2% based on the expectation that intervention will render at least equal - and likely greater- benefit than that detected in a pilot trial previously performed by our group when measured to a threshold POWI >=5 (OR 0.367-0.563, POWI >=4). These results were presented at the 86th Annual Scientific Congress of the Royal Australasian College of Surgeons, May 2017 (Award for Best Scientific Paper), and the full statistical data tables from this trial are available on request. All eligible consenting patients presenting to the Auckland Plastic Surgery Unit over a 3-month period in 2016 were enrolled. Patients were randomly allocated to one of three treatment groups: buffered local anaesthetic (LA); buffered LA with

micro-dosed clindamycin; or buffered LA with micro-dosed flucloxacillin. Solutions were infiltrated to the excision sites (and donor sites if applicable) in double-blinded fashion. Wounds were assessed using the same standardized POWI scoring system employed in the current study at 1 week and 1 month after surgery. The primary outcome was the overall rate of SSIs. Secondary outcomes included adverse events, SSI-associated co-morbidities, culture swabs and antibiotic use. A total of 332 patients were enrolled (519 lesions excised). Treatment groups were comparable at baseline.

The sample size calculations in the table below are based on achievement of 80% power at a 5% level of significance (to which a False Discovery Rate correction has been applied to allow comparison between each of the active treatments and placebo). These infection rate differences (7% vs 2%), and associated sample size are used to guide patient recruitment so that study power is maximized.

Group	Infection Rate - POWI ≥5 (%)	Required Group Size (# Lesions)	Required Sample Size
Placebo	7	299	987
Flucloxacillin	2	344	
Clindamycin	2	344	

In summary, to achieve 80% power with a 5% level of significance (to which a False Discovery Rate correction was applied to allow comparison between each active treatment and control), it was calculated that 987 lesions would need to be recruited.

Framework:

Superiority analysis of interventions versus standard of care (control)

Timing of final analysis:

The final analysis will be performed collectively at completion of data collection (at least 3 weeks following final lesion recruitment).

Confidence intervals and P values:

The level of statistical significance will be at least 0.05, two sided tests.

There will be no adjustments for multiplicity. Not all pairwise comparisons will be made, only the ones defined a-priori. Those comparisons are with the control value, and will only be done after the general test indicates a significant effect.

Confidence intervals to be reported are the 95% confidence intervals

Adherence and protocol deviations:

Any differences between the intended treatment and actual treatment will be prospectively collected and summarily reported at study conclusion.

Outcome definitions:

Primary outcome measure is Surgical Site Infection (SSI) as defined by maximal standardized Post-Operative Wound Infection (POWI) score recorded at any follow up visit, per lesion, with a value greater than or equal to 5 [scale, 0-7], by arm.

Analysis will also be performed by maximal standardized POWI score greater than or equal to 4 by arm

The main outcome of the trial is POWI classified in 7 groups. Depending on the sizes of the group it is possible that adjacent groups will be combined. This will be done by checking the variances of the estimates. When the group size is small, the variances will be large compared to other groups. On medical grounds combining groups 5, 6 and 7 to create a POWI with 5 classes makes sense *a priori.*

Analysis Methods:

Analysis method used and how treatment effects will be presented: the Logistic regression for multinomial observations will be used as described by Dobson and Barnett. Estimated POWI proportions for each treatment arm will be presented in histograms and comparisons between treatments and arms will be calculated on basis of estimated parameters and covariances from the model.

Any adjustment for covariates: Analysis with and without covariate as interaction term. Only baseline characteristics are used as covariate.

The assumptions will be checked by using the methods given in the DHARMa package in "R."

Details of alternative methods to be used if distributional assumptions do not hold, e.g.,normality, proportional hazards: if the assumptions do not hold, then this can maybe solved by adding covariates, assuming different distribution, maybe probit analysis or if all fails using sandwich estimators for the covariances.

Additional Analyses:

Subgroup analyses are defined as adding an interaction term with a covariate (e.g. Age group, surgical location, gender, ethnicity) assuming adequate number of observations in each subgroup

Missing data:

Reporting and assumptions/statistical methods to handle missing data: It is not expected that there will be many missing values. If there are a few missing values and it looks randomly distributed over the treatment arms then they will be ignored. If there are a mediate number of missing values and or biased distribution of those, then we will impute them with the help of the baseline characteristics.

Harms:

Adverse events are coded according to a combination of direct observation by medical staff at all patient encounters (eg, point of intervention and each subsequent assessment), and elicited patient reported outcomes at all patient encounters. These includes signs or symptoms of allergic/hypersensitivity reaction (i.e., localized pruritis, erythema, induration, pain), and/or anaphylaxis (i.e. tachypnea/shortness of breath, wheeze/stridor, tachycardia,

anxiety/confusion, loss of consciousness).

Laws and regulations:

This clinical study will be conducted in compliance with all national laws and regulations of the countries in which the clinical trial is performed, and in strict congruence with good clinical practice (GCP), as well as any additional local applicable guidelines. The trial has been registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR); https://anzctr.org.au/. Trial registration number: ACTRN12616000364471.

Publication and data sharing policy:

The preparation and submittal for publication of manuscripts containing the study results shall be the responsibility of the Principal Investigator (PI), with agreement among final contributing and supporting investigators. The publication and/or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

Conflicts of interest:

No conflicts of interest have been identified. Conflicts will be proactively re-assessed at time of study conclusion and at each event of study publication and/or data sharing and reported as indicated.

Supplements/Appendices:

1. Informed Consent
2. Participant information Sheet
3. Ethics: Central Health and Disability Ethics Committee (HDEC Full Review Pathway; ref 15/CEN/260)
4. Custom PICASSo Study Database (MedSyn Software, Auckland), representative screenshot
5. Full “PICASSo Statistical Analysis Plan” provided as separate Attachment

PLASTIC RECONSTRUCTIVE & HAND SURGERY UNIT

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2025

Consent Form

PROJECT TITLE:
Infiltrating antibiotics to reduce the rate of wound infection

REQUEST FOR INTERPRETER (PLEASE CIRCLE ONE OPTION BELOW)

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu.	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai

1 I have read and I understand the information sheet dated 22nd February 2016 for volunteers taking part in the study designed to investigate whether infiltrating antibiotics into the skin prior to the excision of skin lesions reduces the rate of post-operative wound infection. I have had the opportunity to discuss the study. I am satisfied with the answers I have been given.

2 I have had the opportunity to use whanau support or a friend to help me ask questions and understand the studies.

3 I understand that taking part in these studies is voluntary (my choice) and that I may withdraw from the studies at any time and this will in no way affect my continuing health care.

4 I understand that my participation in these studies is confidential and that no material which could identify me will be used in any reports on these studies.

5 I understand that I can request notification of study results once they become publically available by contacting the Principal Investigator.

6 I have had time to consider whether to take part.

7 I know who to contact if I have any questions about the studies.

8 I wish to receive a summary of the results of the study Yes ☐ No

I …… *(full name or patient label)***……. hereby consent to take part in this study.**

Signature:_____ **Date:** _____

Principal Investigator: Jon Mathy MD FACS **Contact Phone**: (09)276-0044 ext 2680

Contact Email: Jon.Mathy@middlemore.co.nz

Project explained by:_____ **Project Role:** _____

Signature:_____ **Date**:_____

One copy of the Consent Form is to be retained by the participant and a second copy is to be placed in the medical file.

PLASTIC RECONSTRUCTIVE & HAND SURGERY UNIT

Telephone +64 9 276 0135

Jon Mathy MD FACS
Principal Investigator
Senior Lecturer, University of Auckland School of Medicine

Phone: +64 9 276 0044, ext 2680
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100 Hospital Road
Middlemore Hospital
Counties Manukau DHB
Papatoetoe
2025

Information Sheet
for patients undergoing skin surgery

PROJECT TITLE: Infiltrating antibiotics to reduce the rate of wound infections in skin surgery

You are invited to take part in a research study. You have every right to decline to be involved in the research study, and this will not affect your treatment in any way. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve for you.

Please take time to read the following information carefully. You may wish to ask a friend, family or whanau support to help you understand the risks and benefits of this study and any other explanation you may require. You may also wish to discuss the study with your GP or another doctor.

If you need an interpreter to help you understand the study, one can be provided.

ABOUT THE STUDY

1. What are the aims of the study?

Our main aim is to determine whether we can reduce the rate of post-operative wound infections following skin surgery. We plan to infiltrate antibiotics into the skin at the same time as we infiltrate the local anaesthetic.

2. How were the participants selected for this study, and who selected them?

Any patient presenting for skin surgery is eligible for the study as long as they do not meet the exclusion criteria.
Exclusion criteria include the use of antibiotics within two weeks of surgery, or an allergy or adverse reaction to the antibiotic.

3. How many participants will be involved?

In total, the study is expected to involve over 1000 patients.

4. Where will the study be held?

The study will take place at Counties Manukau District Health Board and be run by staff from the Plastic Surgery Department in conjunction with the Infectious Diseases department.

5. What is the timespan of the study?

The study will last a total of 9 months.

6. What will happen during the study?

If you decide to take part, you will be asked to sign a Consent Form. The time requirement for the study is small – apart from reading this Information Sheet and Consent Form, the procedure itself (your skin surgery) will take no longer than typical.

At the time of your surgery, you will be randomly assigned to receive either local anaesthetic (standard) or local anaesthetic with antibiotic mixed in. Neither you nor the surgeon will know which group you have been allocated to. You will then undergo your operation; taking part in the study will not alter your surgical treatment.

We will arrange follow up with one of our nursing staff to take place between 5-10 days after your operation. Sutures will be removed and the wound will be assessed for any evidence of infection. This appointment will save you a trip to your GP to have any sutures removed. You will then receive a second appointment to take place around 3-4 weeks after your operation for further review of your operative site and surgery results once your tissue has been fully examined under the microscope.

BENEFITS, RISKS and SAFETY

7. What are the benefits of the study?

If you agree to participate in the study and are randomised to receive incisional antibiotics, you may benefit by a reduced infection rate compared to someone undergoing the same surgery without incisional antibiotics. Patients recovering from skin surgery without infection generally experience faster healing with less pain, less wound care, and improved final wound appearance compared to patients who develop infections after their surgery.

Neither you nor your surgeon will know if you received incisional antibiotics or not. However, the results of this study will help determine if and when other people undergoing skin surgery will benefit from incisional antibiotics, and whether changing routine practice to include incisional antibiotics will improve outcomes and lower costs of skin surgery throughout New Zealand and internationally.

8. What are the risks or inconveniences of the study?

If you agree to participate in the study and are randomised to receive incisional antibiotics, you may experience a higher rate of allergic or sensitivity reactions to the antibiotics compared to someone undergoing the same surgery without incisional antibiotics. For example, you may experience rash, irritation, itching, or swelling around the surgery site. These reactions typically require no additional treatment and would be expected to resolve on their own over the course of 24 hours.

As with any antibiotic usage, there is also a small chance of experiencing an anaphylactic reaction, which can be a serious and life-threatening reaction without further treatment. An anaphylactic reaction would typically occur immediately after injection by your surgeon and would require additional treatments by your surgical team such as an injection of adrenaline to reverse the reaction followed by a period of monitoring before leaving hospital.

Participation in the study will not result in any monetary cost to you in any way. In fact, participation will save you an appointment with your GP to take the sutures out. We will need to see you between 5-10 days and about 3 weeks after the operation which may be of inconvenience.

If you experience any questions or concerns requiring immediate attention at any point after your skin surgery you can ring 111 for immediate advice or return to see a member of the skin surgery team 24 hours a day/7 days a week/365 days a year through our emergency room located at Middlemore Hospital. For all other concerns or queries please feel free to contact our Principal Investigator (contact details above). Additionally, we will be reviewing your progress in person between 5-10 days and about 3 weeks after the operation.

YOUR PARTICIPATION IN THE STUDY

9. If you do decide to take part, can you change your mind later?

You can refuse to present for follow up if you so wish, however, follow up is part of the standard follow up practice after skin surgery.

10.What will happen if you decide not to take part?

Your participation is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part you will receive the usual treatment and care. You do not need to give any explanation if you decide not to take part – this decision is entirely your own choice, and will be fully respected.

11. Will your participation be confidential?

Your participation will be confidential, and all information collected about you during the course of the research will also be kept strictly confidential. If you consent to take part in the study, we will need to record some details of your medical history for the purpose of analysing our results. These details include whether you are allergic to flucloxacillin or clindamycin, whether you are a smoker, diabetic or immunosuppressed, and whether you have experienced a prior surgical site infection. The data collected will be kept secure on our hospital computer system and be password protected.

12. Will you be informed about the results of the study?

You will not receive any individual results. However, a summary of the study findings will be sent to all participants who indicated they wished to receive them on the consent form. We aim to publish the results of our research in a leading scientific or medical journal with a particular focus on skin lesions or infections, and we also aim to keep the public informed of our work through the media. You are also welcome to contact the Principle Investigator to discuss the study outcomes, although it is important to realise that it may take many months to reliably determine these outcomes.

13. Does the study involve any genetic testing?

This study does not involve any genetic testing.

FOR MORE INFORMATION

14. Do you have any more questions for the researchers?

Please feel free to contact the study's Principal Investigator, Mr Jon Mathy, whose contact details appear above.

15. Would you like some independent advice?

If you have any questions or concerns about your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

Telephone (NZ wide): 0800 555 050
Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)
Email (NZ wide): advocacy@hdc.org.nz

The Whanau Support Team at Middlemore Hospital is also available to provide further advice. Contact person is: Betty Lou Iwikau, Service Manager Maaori Health Services
Telephone: 09 276 0044 extension 9079
Email: IwikauB@middlemore.co.nz

STATEMENT OF APPROVAL

This study has been reviewed and approved by the Central Health and Disability Ethics Committee through the HDEC-Full Review pathway.

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

FINALLY …

Thank you for reading this and considering participation in the study.

Health and Disability Ethics Committees
Ministry of Health
Freyberg Building
20 Aitken Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@moh.govt.nz

14 March 2016

Mr Jonathan Mathy
Department of Plastic Reconstructive & Hand Surgery
Middlemore Hospital
100 Hospital Road
Papatoetoe 2025

Dear Mr Mathy

Re:	**Ethics ref:**	**15/CEN/260**
	Study title:	Incisional antibiotic prophylaxis to prevent postoperative wound infections in skin cancer surgery

I am pleased to advise that this application has been *approved* by the Central Health and Disability Ethics Committee. This decision was made through the HDEC-Full Review pathway.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Central Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.

2. Before the study commences at *any* locality in New Zealand, it must be registered in a clinical trials registry. This should be a WHO-approved (such as the Australia New Zealand Clinical Trials Registry, www.anzctr.org.au). However https://clinicaltrials.gov/ is acceptable provided registration occurs prior to the study commencing at *any* locality in New Zealand.

3. Before the study commences at *a given* locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

5. 18-656-Mathy - PICASSo Trial - HDEC approval document

Non-standard conditions:

- The Committee recommends the amendment of section 12 of the Participant Information Sheet so that it states that participants will receive a summary of the study results rather than having to request them once they become publicly available.

  The Consent form should be changed as well to reflect this. The following line can be used and the yes/no option should be included to clearly indicate that the statement is truly optional.

I wish to receive a summary of the results from the study. Yes ☐ No ☐

Non-standard conditions must be completed before commencing your study. Non-standard conditions do not need to be submitted to or reviewed by HDEC before commencing your study.

If you would like an acknowledgement of completion of your non-standard conditions letter you may submit a post approval form amendment. Please clearly identify in the amendment that the changes relate to non-standard conditions and ensure that supporting documents (if requested) are tracked/highlighted with changes.

For information on non-standard conditions please see section 128 and 129 of the Standard Operating Procedures at http://ethics.health.govt.nz/home.

After HDEC review

Please refer to the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.

Your **next progress report** is due by **13 March 2017.**

Participant access to ACC

The Central Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation (ACC).

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Mrs Helen Walker
Chairperson
Central Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix A

Documents submitted

Document	*Version*	*Date*
CV for CI: CV for LI	1	04 November 2015
Investigator's Brochure: Information sheet for patients	1.0	28 November 2015
PIS/CF: Consent form	1.0	28 November 2015
Evidence of CI indemnity	1.0	30 November 2015
Covering Letter: Cover letter	1.0	30 November 2015
Evidence of scientific review: Evidence of scientific review	1.0	30 November 2015
Protocol: Protocol	1.0	30 November 2015
PIS/CF: Patient Information Sheet	1.1	16 December 2015
Consent Form	1.1	16 December 2015
Application		
Evidence of scientific review		
PIS/CF: Amended Information Sheet as per instructions from HDEC review	2.0	22 February 2016
PIS/CF: Amended Consent Form as per HDEC review	2.0	22 February 2016
Response to Request for Further Information		23 February 2016

Appendix B

Statement of compliance and list of members

Statement of compliance

The Central Health and Disability Ethics Committee:

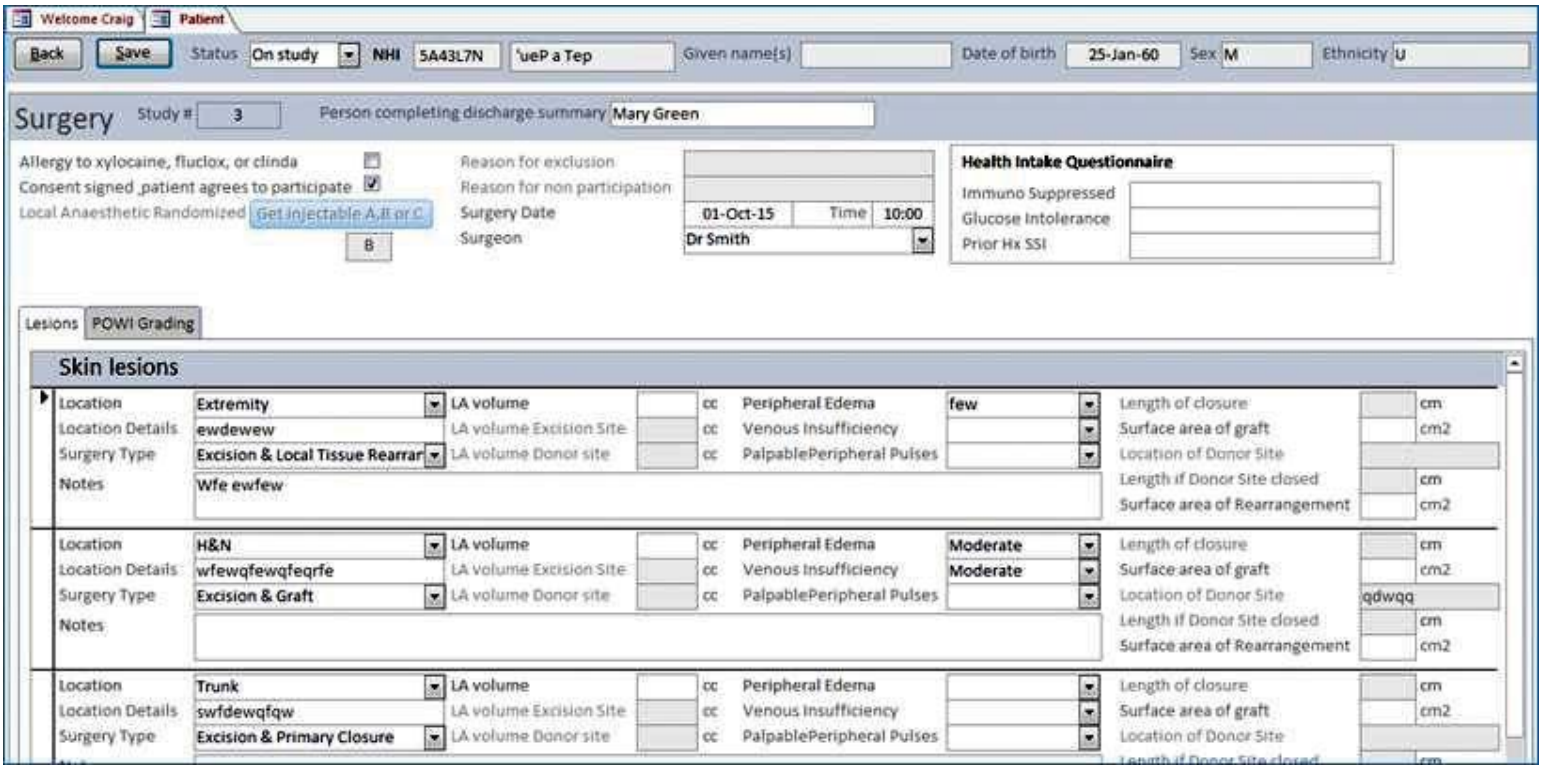
- is constituted in accordance with its Terms of Reference
- operates in accordance with the *Standard Operating Procedures for Health and Disability Ethics Committees*, and with the principles of international good clinical practice (GCP)
- is approved by the Health Research Council of New Zealand's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990
- is registered (number 00008712) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

Name	*Category*	*Appointed*	*Term Expires*
Mrs Helen Walker	Lay (consumer/community perspectives)	01/07/2015	01/07/2018
Dr Angela Ballantyne	Lay (ethical/moral reasoning)	30/07/2015	30/07/2018
Dr Melissa Cragg	Non-lay (observational studies)	30/07/2015	30/07/2018
Dr Peter Gallagher	Non-lay (health/disability service provision)	30/07/2015	30/07/2018
Mrs Sandy Gill	Lay (consumer/community perspectives)	30/07/2015	30/07/2018
Dr Patries Herst	Non-lay (intervention studies)	27/10/2015	27/10/2018
Dr Dean Quinn	Non-lay (intervention studies)	27/10/2015	27/10/2018
Dr Cordelia Thomas	Lay (ethical/moral reasoning)	19/05/2014	19/05/2017

Unless members resign, vacate or are removed from their office, every member of HDEC shall continue in office until their successor comes into office (HDEC Terms of Reference)

http://www.ethics.health.govt.nz


Welcome Craig
Patient
Back
Save
Status On study
NHI 5A43L7N
'ueP a Tep
Given name(s)
Date of birth 25-Jan-60
Sex M
Ethnicity U
Surgery
Study # 3
Person completing discharge summary Mary Green
Allergy to xylocaine, fluclox, or clinda
Consent signed ,patient agrees to participate
Local Anaesthetic Randomized
Get injectable A,B or C
B
Reason for exclusion
Reason for non participation
Surgery Date 01-Oct-15 Time 10:00
Surgeon Dr Smith
Health Intake Questionnaire
Immuno Suppressed
Glucose Intolerance
Prior Hx SSI
Lesions
POWI Grading
Skin lesions
Location Extremity
Location Details ewdewew
Surgery Type Excision & Local Tissue Rearrar
Notes Wfe ewfew
LA volume
LA volume Excision Site
LA volume Donor site
cc
Peripheral Edema few
Venous Insufficiency
PalpablePeripheral Pulses
Length of closure cm
Surface area of graft cm2
Location of Donor Site
Length if Donor Site closed cm
Surface area of Rearrangement cm2
Location H&N
Location Details wfewqfewqfeqrfe
Surgery Type Excision & Graft
Notes
LA volume
LA volume Excision Site
LA volume Donor site
cc
Peripheral Edema Moderate
Venous Insufficiency Moderate
PalpablePeripheral Pulses
Length of closure cm
Surface area of graft cm2
Location of Donor Site qdwqq
Length if Donor Site closed cm
Surface area of Rearrangement cm2
Location Trunk
Location Details swfdewqfqw
Surgery Type Excision & Primary Closure
LA volume
LA volume Excision Site
LA volume Donor site
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Peripheral Edema
Venous Insufficiency
PalpablePeripheral Pulses
Length of closure cm
Surface area of graft cm2
Location of Donor Site