ROSSINI-PLATFORM TRIAL

Pillar-Specific Protocol

VASCULAR LOWER LIMB AMPUTATION

A 'Basket Factorial MAMS' Platform Trial in Surgical Site Infection

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2025)

Version Number: **1.0**

Version Date: **05-Jan-2026**

VASCULAR LOWER LIMB AMPUTATION PILLAR SPECIFIC PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

Funding and support in kind	
Funder(s)/Supporting Organisations	**Financial and non-financial support given:**
National Institute of Health and Care Research (NIHR)	Financial, Investigator led grant
Funding scheme	NIHR Health Technology Assessment (HTA) Programme
Funder's reference number	NIHR163832
The funder of the trial will have no role in the trial design, data collection, data analysis or data interpretation, or in the writing of the final report; and the decision to submit the report for publication. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.	

SUPPLIERS
Provision of intervention

PROTOCOL SIGN OFF

Pillar Lead for Lower Limb Amputation - Signature Page

I, the Pillar Lead, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	ROSSINI-Platform (LOWER LIMB AMPUTATION Pillar)
Protocol version number:	Version: __ __
Protocol version date:	__ __/__ __ __/__ __ __ __
Pillar lead name:	Mr David Bosanquet
Signature and date:	_____ __ __/__ __ __/__ __ __ __

Sponsor statement

By signing the IRAS form for this trial, the University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the VASCULAR LOWER LIMB AMPUTATION Pillar within the ROSSINI-Platform trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the Vascular Lower Limb Amputation Pillar of the ROSSINI-Platform trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, the Medicines for Human Use (Clinical Trials) Regulations 2004, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and Mental Capacity Act 2005, and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name:	ROSSINI-Platform (LOWER LIMB AMPUTATION Pillar)
Protocol version number:	Version: __ __
Protocol version date:	__ __ /__ __ __ /__ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __ /__ __ __ /__ __ __ __

ADMINISTRATIVE INFORMATION

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TBC	Patient and Public Involvement Representative

ABBREVIATIONS

Abbreviation	Term
BCTU	Birmingham Clinical Trials Unit
CDWH	Centralised Digital Wound Hub
ciNPWT	Closed incision Negative Pressure Wound Therapy
CI	Chief Investigator
CKD	Chronic Kidney Disease
eCRF	Electronic Case Report Form
ETMG	Executive Trial Management Group
GCP	Good Clinical Practice
HRA	Health Research Authority
ISF	Investigator Site File
LLA	Lower Limb Amputation
MAMS	Multi Arm Multi Stage
MLLA	Major Lower Limb Amputation
MP	Master Protocol
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator
PSP	Pillar Specific Protocol
RAG	Red-Amber-Green
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
SSI	Surgical Site Infection
TMA	Transmetatarsal Amputation
TKA	Through Knee Amputation
TSC	Trial Steering Committee
UK	United Kingdom
WHO	World Health Organization

ROSSINI PLATFORM: LOWER LIMB AMPUTATION PILLAR TRIAL SUMMARY

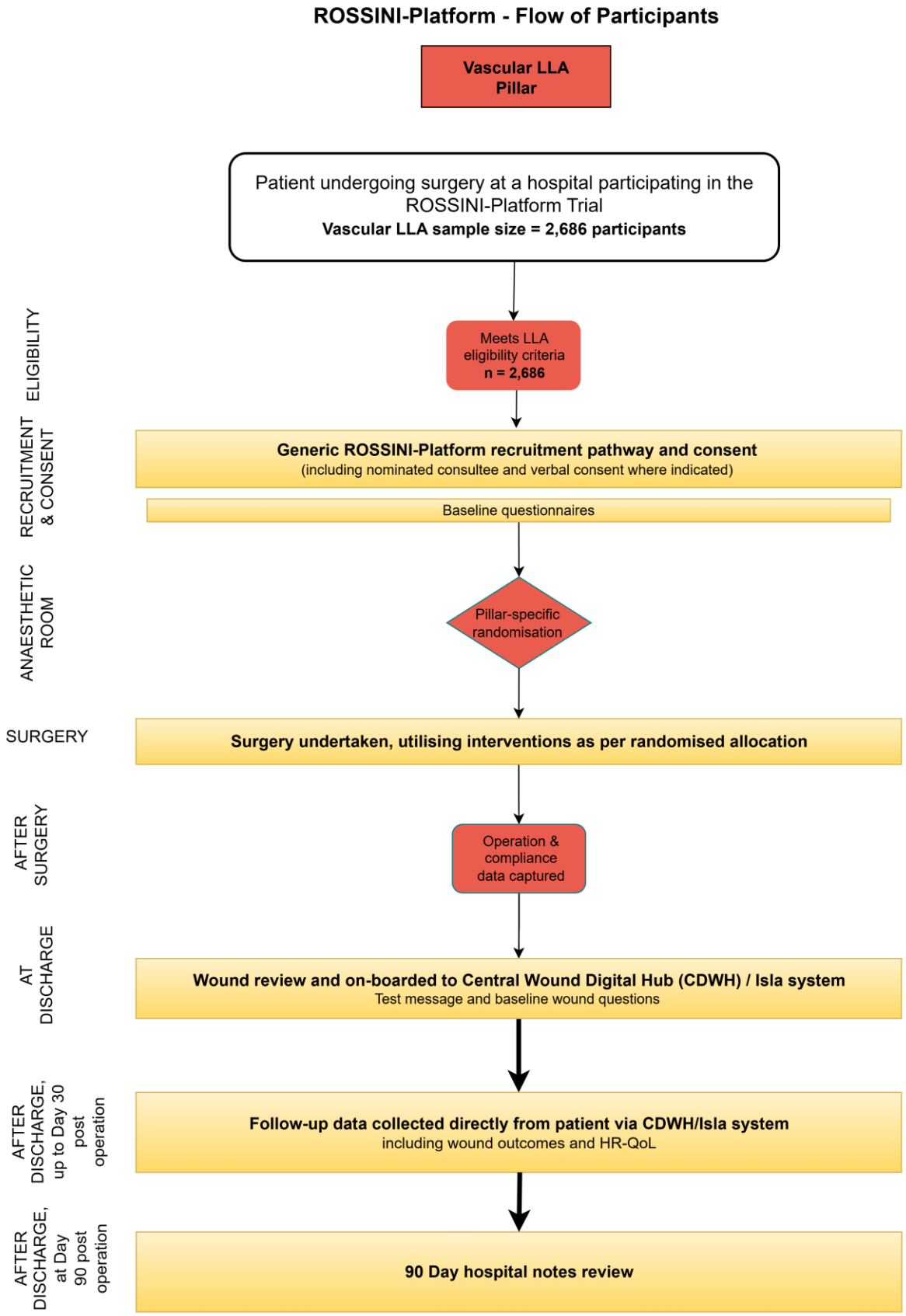
INTERVENTIONS	1. Double skin preparation with 2% alcoholic chlorhexidine followed by an alcoholic iodine solution 2. Subcuticular continuous skin closure with an absorbable suture 3. Closed incision negative pressure wound therapy (ciNPWT) as a dressing applied in theatre
PARTICIPANT POPULATION AND SAMPLE SIZE	Adults undergoing lower limb amputation (LLA) performed by a vascular surgeon, with intent to close the wound primarily. Sample size: 2,686
PILLAR-SPECIFIC ELIGIBILITY CRITERIA **INCLUSIONS**	**Inclusion criteria;** • Patients aged 16 and over undergoing elective or emergency LLA (transmetatarsal amputation (TMA), transtibial amputation, through knee amputation (TKA), or transfemoral amputation) with intent to close the wound primarily by a vascular surgeon • Reintervention procedures that are intended to close the wound primarily, inclusive of: ○ Revision amputation – i.e. revision surgery at the same amputation level (with or without bone resection) ○ Reamputation –i.e. to a higher amputation level • Patients who have previously been entered into the trial are eligible for recruitment for amputation procedures meeting the above inclusion criteria (contralateral amputation or revision amputation/reamputation procedure) provided the index procedure is performed at least 90 days following the previous randomisation.
PILLAR-SPECIFIC ELIGIBILITY CRITERIA **EXCLUSIONS**	**Exclusion criteria;** • Patients undergoing digital amputation, disarticulation of the hip, or hindquarter amputation. • Amputation where there is no intention to close the fascial and skin layers (e.g. a guillotine amputation) • **For intervention 1: Double skin preparation** ○ Known allergy to 2% alcoholic chlorhexidine ○ Known allergy to iodine • **For intervention 2: Skin closure with continuous subcuticular suture** ○ Known allergy to the available sutures used for subcuticular closure

	• **For intervention 3: Closed incision negative pressure wound therapy [ciNPWT]**
	  ○ Known allergy to material within the adhesive dressing used to deliver ciNPWT
	  ○ Frail/fragile skin that is liable to tearing

PILOT TARGETS	Green progression criteria at internal pilot:
	AT PILLAR LEVEL
	• Site activity
	  ○ Green criterion: ≥8 sites active
	• Participant recruitment
	  ○ Green criterion: ≥40 patients recruited
	• Completion of CDWH
	  ○ Green criterion: Engagement with Centralised Digital Wound Hub (CDWH) for ≥95% of recruited patients
	• Patient level data sent to Birmingham Clinical Trials Unit (BCTU)
	  ○ Green criterion: Baseline data sent to BCTU for ≥95% of recruited patients
	AT INTERVENTION LEVEL
	• Compliance with randomised allocation by surgeon
	  ○ Green criterion: Compliance for ≥95% of recruited patients
	• For each intervention: Level of acceptance of randomisation in proportion to other interventions in the pillar
	  ○ Green criterion: Acceptance for ≥80% as a proportion of patients recruited to other interventions

TIMELINES	Up to 50 months of recruitment.

TRIAL SCHEMA



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1. PILLAR SPECIFIC PROTOCOL STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While, all adaptations are pre-specified (the dropping or addition of interventions/pillars), the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new interventions or pillars or both.

The protocol has multiple modules comprising the ROSSINI-Platform Master Protocol, overview and design features of the study) and multiple Pillar-Specific Protocols (PSP) (detailing all interventions currently being studied in each Pillar).

The Master Protocol contains all information that is generic to the trial, irrespective of the pillars or interventions that are being tested. The Master Protocol may be amended but it is anticipated that such amendments will be infrequent. The Master Protocol does not contain information about the intervention(s), within each pillar as one of the trial adaptations is the change of interventions over time.

Information about interventions, within each pillar, is covered in a PSP. These PSPs are anticipated to change over time, with removal and addition of options within an existing pillar. Each substantial modification to a PSP will require regulatory approval.

The Master Protocol does not contain detailed information about the statistical analysis, but this information is contained within the Statistical Analysis Plan (SAP).

2. BACKGROUND AND RATIONALE

2.1 Pillar definition

This is a Pillar within the ROSSINI-Platform Trial to test the effectiveness of specific peri-operative interventions to prevent Surgical Site Infections (SSI) in patients undergoing elective or emergency lower limb amputation by a vascular surgeon.

2.2 Pillar-specific background

Lower Limb Amputation (LLA) including Major Lower Limb Amputation (MLLA, defined as an amputation of the lower limb above the level of the ankle joint) and transmetatarsal amputation (TMA) are treatment options to deal with complications of peripheral arterial disease, diabetes mellitus, trauma, or cancer. In the United Kingdom (UK), complications of peripheral arterial disease

and/or diabetes mellitus is by far the most common indication for this procedure, the number of MLLA performed each year for this indication is approximately 3,500.

An observational study completed and presented at the United Kingdom Vascular Societies' Annual Scientific Meeting in 2024 aiming to define a contemporaneous rate of MLLA SSI reported this to be 14% based on data from 614 patients from 45 centres. A systematic review on SSI incidence after MLLA demonstrated that reported rates range from 7.1% to 39.5%.[1] This review identified that randomised controlled trials (RCT) (in particular higher quality RCTs) yielded a higher SSI rate, the pooled rate from the control arms of trials that included patients with peripheral arterial disease and/or diabetes mellitus was 15.3%. The only RCT conducted in the UK reported that 25.6% of MLLAs and 30.8% of TMAs developed SSIs.[2]

SSI and failure of wound healing can lead to revision surgery, in addition to medical morbidity and mortality. Frequently this means conversion of a TMA to an amputation above the ankle, or a transtibial amputation to a transfemoral amputation.[2] This has profound consequences for rehabilitation/ambulation; patients may be rendered wheelchair-bound rather than ambulating with a prosthetic limb and patients could require residential care rather than be living independently. These are known contributors to social isolation and psychological morbidity.[3-5] Whilst all SSIs can carry significant morbidity, social isolation and the impact on psychological morbidity, means wound healing after LLA is critical.

This pillar within the ROSSINI Platform will evaluate three peri-operative interventions that aim to reduce SSI following LLA. The three interventions being evaluated are: double skin preparation versus single skin preparation, subcuticular continuous skin closure versus interrupted transdermal skin closure, and closed incision negative pressure wound therapy (ciNPWT) versus standard practice dressing.

2.3 Pillar-specific rationale

2.3.1 Justification for pillar-specific participant population

The most common indication for LLA in the UK is complication of peripheral arterial disease and/or diabetes mellitus. A considerable proportion of LLAs performed for this indication are performed during unscheduled admissions to hospital. Patients requiring urgent/emergency LLA will differ in some regards to those requiring planned/elective LLA, however the underlying pathology and demographics of these groups are similar. Potential differences in baseline characteristics between the two groups that are relevant to SSI include concurrent infection in the index limb – which is a minimisation factor in the randomisation process for this pillar. Consequently, the inclusion of both urgent/emergency and planned/elective LLA in this pillar is justified.

Two other, much less common, indications for LLA are trauma and cancer. Patients undergoing LLA for these indications are likely to differ in their baseline characteristics to those with complications

of peripheral arterial disease and/or diabetes mellitus. There is less data available on LLA outcomes for these patients, but the impact of SSIs on wound healing and sequalae such as revision surgery, less ambulation/independence are considered just as detrimental to these patient groups, therefore their inclusion was judged to be valuable.

2.3.2 Justification for choice of interventions

Intervention 1: Double skin preparation

In this pillar, double skin preparation consists of an initial skin preparation with 2% alcoholic chlorhexidine followed by a second skin preparation with an alcoholic iodine solution. The control arm is single skin preparation (solution determined by operating surgeon). Evidence concerning skin preparation before LLA is scant and is based on observational data only. Randomised data from patients undergoing total joint arthroplasty suggests double skin preparation reduces SSI rates significantly.[6] Whilst studies are limited, a systematic review suggests double skin preparation increases bacterial decolonization at the incision site, compared to single skin preparation.[7] It is purported that the difference in clinical outcome is due to alcoholic chlorhexidine and alcoholic betadine solutions having different mechanisms, onset, and duration of action.[8]

Intervention 2: Skin closure with continuous subcuticular suture

There is uncertainty whether using continuous subcuticular or interrupted closure affects SSI incidence.[9] In vascular surgery, observational studies have suggested that the use of skin clips could be associated with a higher SSI risk.[10] Interventional studies have conflicting results, but evidence is lacking in quality and quantity, and up-to-date randomised evidence specific to LLA is needed.[11]

Intervention 3: Closed incision negative pressure wound therapy (ciNPWT)

This intervention has evidence to support its use in certain high-risk vascular surgery wounds,[11] but no high-quality evidence in LLA. A systematic review identified 3 observational studies (457 patients) looking at ciNPWT in MLLA and showed reduced SSI rates when compared to standard practice.[12]

3. PILLAR SPECIFIC PILOT AIMS AND OBJECTIVES

3.1 Internal pilot objectives

The trial includes a 3-month internal pilot phase at Platform, Pillar and Intervention level.

The pilot phase of the vascular LLA pillar will begin when the first patient is recruited to the pillar. The pilot phase will inform decisions on the continuation of the trial. The aims of the internal pilot at Pillar level are to assess:

- Number of sites opened
- Number of patients recruited

- Engagement with the CDWH
- Participant-level data at BCTU

At the end of the internal pilot phase, the Executive Trial Management Group (ETMG) and Trial Steering Committee (TSC) will review the pilot data against a set of pre-specified Red-Amber-Green (RAG) criteria:

Table 1: PILLAR Level Internal Pilot Progression Criteria

Progression Criteria	Number of sites opened	Participant recruitment	Engagement with CDWH*	Patient-level data at BCTU**
GREEN (GO)	≥ 8 sites	≥ 40 participants	≥ 95%	≥ 95%
AMBER (modify)	4 -7 sites	11 – 39 participants	≥ 90 - < 95%	≥ 90 - < 95%
RED (STOP)	≤ 3 sites	≤ 10 participants	< 90%	< 90%

* Percentage of participants submitting at least one response to CDWH
**Percentage of participants submitting baseline data to BCTU

Table 2: INTERVENTION-LEVEL Internal Pilot Progression Criteria

Progression Criteria	Compliance with randomised allocation by surgeon	Relative clinician acceptance of each intervention within the pillar[+]
GREEN (GO)	≥ 95%	≥ 80%
AMBER (modify)	≥ 85 - < 95%	≥ 60 - < 80%
RED (STOP)	< 85%	< 60%

[+] measured as willingness to accept it divided by its availability, considering site provision and participant eligibility prior to randomisation.

Intervention-level progression criteria relate to all interventions.

At the end of the first 3-month pilot, a second 3-month internal pilot can be triggered if deemed necessary by the Trial Steering Committee.

4. TRIAL DESIGN AND SETTING

4.1 Trial design

The LLA Pillar will be conducted as part of the ROSSINI-Platform trial (See Master Protocol). ROSSINI-Platform is a Basket Factorial Multi Arm Multi Stage (MAMS) platform trial with multiple phase III factorial MAMS RCTs running in parallel. The LLA Pillar represents one of the phase III factorial MAMS RCTs.

4.2 Trial setting

The LLA Pillar will open in approximately 25 NHS trusts in the UK.

5. PILLAR-SPECIFIC ELIGIBILITY

5.1 Inclusion criteria

- Patients aged 16 and over undergoing LLA (transmetatarsal amputation (TMA), transtibial amputation, through knee amputation (TKA), or transfemoral amputation) with intent to close the wound primarily by a vascular surgeon
- Reintervention procedures that are intended to close the wound primarily are also included, which are inclusive of:
    - Revision amputation – i.e. revision surgery at the same amputation level (with or without bone resection)
    - Reamputation – i.e. to a higher amputation level
- Patients who have previously entered the trial are eligible for recruitment for amputation procedures meeting the above inclusion criteria (contralateral amputation or revision amputation/reamputation procedure) provided the index procedure is performed at least 90 days following the previous randomisation.

5.2 Exclusion criteria

- Patients undergoing digital amputation, disarticulation of the hip, or hindquarter amputation.
- Amputation where there is no intention to close the fascial and skin layers (e.g. a guillotine amputation)
- For intervention 1: **Double skin preparation**
    - Known allergy to chlorhexidine
    - Known allergy to iodine
- For intervention 2: **Skin closure with continuous subcuticular suture**
    - Known allergy to the available sutures used for subcuticular closure

- For intervention 3: **Closed incision negative pressure wound therapy [ciNPWT]**
    - Known allergy to material within the adhesive dressing used to deliver ciNPWT
    - Frail/fragile skin that is liable to tearing (such that treatment with ciNPWT is deemed inappropriate by the clinical team).

5.3 Co-enrolment

Patients who have been recruited to another RCT examining an intervention that does not share a common biological pathway with impact on the primary outcome measure, are permitted to be included within this pillar.

Sites should contact the ROSSINI-Platform Trials Office to discuss co-enrolment prior to patient recruitment.

6. PILLAR SPECIFIC CONSENT CONSIDERATIONS

Most patients undergoing surgery for LLA will be able to provide fully informed consent for entry into the ROSSINI-Platform trial.

The process for informed consent is detailed within the Master Protocol and the options for provision of informed consent are described and should be followed for this pillar.

It is anticipated that most patients will provide face to face consent either on paper or electronically, however, any method of consent as detailed in the Master protocol is acceptable.

The specific consent considerations for this pillar are:

- Patients that experience a change in clinical condition between recruitment and the date of procedure.
    a. Patients who undergo LLA are often comorbid and frail, and their procedures are often performed during unscheduled admissions to hospital. There is a risk that patients have a change in cognitive function (e.g. due to acute delirium) during the recruitment period which could impact on their capacity to provide informed consent. To increase inclusivity and mitigate the impact on recruitment, the platform protocol details the process of facilitating the inclusion of patients that are unable to provide informed consent.

7. RANDOMISATION and BLINDING

It is possible that patients recruited to this pillar will have a change to their clinical condition (e.g. spreading infection or change to limb perfusion) that will result in them receiving a different procedure to that which they were originally planned to have. This could include a more proximal amputation than originally planned or an amputation procedure that no longer satisfies the inclusion/exclusion criteria (e.g. guillotine amputation, or debridement procedure where the fascia

and skin are deliberately not closed). To reduce the likelihood of this occurring, randomisation will occur as close to the time of surgery as possible.

7.1 Randomisation method

There are three interventions being tested in this pillar. Participants will be randomised in a 1:1 ratio separately for each intervention.

Intervention 1 randomisation:

- Double skin preparation with 2% alcoholic chlorhexidine followed by an alcoholic iodine solution (intervention)
- Single skin preparation with a solution chosen by the operating surgeon (control)

Intervention 2 randomisation:

- Subcuticular continuous skin closure with an absorbable suture (intervention)
- Interrupted skin closure with material (e.g. monofilament suture or skin clips) chosen by the operating surgeon (control)

Intervention 3 randomisation:

- Closed incision negative pressure wound therapy (ciNPWT) as a dressing applied in theatre (intervention)
- Other dressing constituting standard practice chosen by the operating surgeon (control)

A minimisation algorithm will be used within the randomisation system to ensure balance in the intervention allocations over the following variables:

- Centre
- Amputation level (TMA, BKA, TKA, AKA)
- Open wound and/or active infection ((e.g. wound infection/osteomyelitis/infected prosthesis) in the index limb (Yes OR No)
- Diabetes (Yes (on medical therapy not including insulin) OR Yes (on insulin) Yes (Diet controlled) OR No)
- End stage renal disease (CKD 5) (Yes OR No)
- Urgency of surgery (Emergency OR Elective)

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

7.2 Blinding – Additional pillar-specific measures

Within the LLA Pillar, only those participants entered into the intervention 1 randomisation, double skin preparation versus single skin preparation, will be blinded to allocation.

8. PILLAR SPECIFIC TRIAL INTERVENTIONS

As a pragmatic RCT, ROSSINI-Platform does not mandate a specific bundle of care for the prevention of SSI as part of usual care in each trial centre, as this would limit wider generalisability of the findings.

Instead, it is stipulated that all trial sites should adhere to a minimum set of policies as per the National Institute for Health and Care Excellence NICE guidance CG74 (24) on the prevention of SSI. This includes:

- The monitoring and maintenance of normothermia
- Use of a standard three-stage World Health Organization (WHO) Surgical Safety Checklist.

8.1 Standard care

For all patients undergoing LLA within this trial, antibiotic prophylaxis with a minimum of one dose of intravenous antibiotic (specific antibiotic(s) will be chosen by the operating surgeon) will be administered up to 1 hour before the start of surgery.

Extended antibiotic prophylaxis regimes are permitted in each arm of this pillar, including intravenous or oral antibiotics used just for SSI reduction post LLA. Intra-operative use of local antibiotics (direct wound antibiotic delivery e.g. antibiotic impregnated collagen or antibiotic beads) are also permitted.

Each patient will receive single skin preparation with a solution of the operating surgeon's choice (e.g. chlorhexidine or povidone-iodine in aqueous or alcoholic solution), unless randomised to one of the following intervention arms of the trial: 'Double skin preparation with 2% alcoholic chlorhexidine followed by an alcoholic iodine solution'.

The use of torniquets, bone wax, surgical drains or perineural catheters are permitted in every arm of the trial and will be used at the discretion of the operating surgeon.

Exact technique of the LLA, including how the bone is divided (if applicable), and fascial layer closure will be performed using a method at the operating surgeon's discretion. Only patients randomised to receive the trial intervention of ciNPWT should receive this therapy at the time of surgery.

8.2 Trial interventions

Intervention 1: Double skin preparation with 2% alcoholic chlorhexidine followed by an alcoholic iodine solution

For surgical procedures involving a skin incision, a solution with bactericidal properties is used to 'prepare' the skin – whereby skin-dwelling organisms are killed aiming to create a sterile operating field and reduce SSI. Common solutions used for this purpose are chlorhexidine or iodine in alcohol or aqueous solutions.

This intervention describes using two specified solutions for skin preparation, in a specific order of use. The first solution will be 2% alcoholic chlorhexidine (e.g. 'Chloraprep TM' applicator). Following application, users will allow time for the solution to dry according to the manufacturer's recommendation for use. Next, an iodine in alcohol solution will be applied and allowed to dry as per the manufacturers' instruction for use before making a skin incision.

Any 2% alcoholic chlorhexidine applicators/solutions are permitted for patients randomised to this intervention and can be based on the operating surgeon's preference.

Comparator: Single skin preparation with a solution chosen by the operating surgeon (control)

Intervention 2: Subcuticular continuous skin closure with an absorbable suture

This intervention describes a method of skin closure whereby an absorbable suture placed entirely within the subcuticular layer is used to approximate the skin edges. Other methods of approximating the skin edges (such as continuous or interrupted transdermal sutures or skin clips) are not permitted for patients allocated to this intervention.

Comparator: Interrupted skin closure with material (e.g. monofilament suture or skin clips) chosen by the operating surgeon (control)

Intervention 3: Closed incision negative pressure wound therapy (ciNPWT) as a dressing applied in theatre

This intervention describes the application of a dressing and device combination that aims to deliver continuous negative pressure therapy to a closed wound at the end of surgery. After closing, cleaning, and drying the skin, the dressing and device combination will be applied in theatre. There are adjuncts to ciNPWT that aim to aid in the successful application and maintenance of an airtight seal that are permitted if patients are allocated to this intervention. These adjuncts include (but are not limited to) skin preparation wipes, solutions, or tapes/film (e.g. Cavalon film or Duoderm) and additional adhesive strips placed along the edges of the dressing.

This intervention aims to evaluate ciNPWT as a therapy concept rather than evaluate any individual trademarked device. Our industry partner will provide ciNPWT devices to sites throughout the duration of the trial.

Other ciNPWT devices are permitted for patients randomised to this intervention.

Sites may have a pre-existing supplier of ciNPWT devices, it is anticipated that sites will utilise the devices supplied by our industry partner but can rely on any existing stock they may hold in any scenario where stock from the trial supplier are unavailable or based on the operating surgeon's preference.

The duration of ciNPWT should be guided by the manufacturer's instruction for use. The duration of therapy delivered (in days) and the number of times the dressing was reapplied to achieve an adequate seal will be recorded for each patient randomised to this intervention.

Comparator: Other dressing constituting standard practice (not ciNPWT) chosen by the operating surgeon (control)

8.3 Contraindications

Specific contraindications to each intervention are:

Intervention 1: Double skin preparation with 2% alcoholic chlorhexidine followed by an alcoholic iodine solution

The contraindications to this intervention are:

- Known allergy to chlorhexidine
- Known allergy to iodine

Intervention 2: **Subcuticular continuous skin closure with an absorbable suture**

The contraindications to this intervention are:

- Known allergy to the available sutures used for subcuticular closure

Intervention 3: Closed incision negative pressure wound therapy (ciNPWT) as a dressing applied in theatre

The contraindications to this intervention are:

- Known allergy to material within the adhesive dressing used to deliver ciNPWT
- Frail/fragile skin liable to tearing

8.3.1 Concomitant medication(s)/intervention(s)

Not applicable.

8.3.2 Prohibited medication(s)/intervention(s)

Not applicable.

8.4 Intervention modification or discontinuation

Any instances where a patient with no known relevant allergies experiences a suspected allergic reaction to any of the listed interventions, discontinuation of the intervention should be immediate and reported to the trial team as a SAE.

It is anticipated that for some patients allocated to the ciNPWT intervention, there may be periods during the intended therapy duration where an adequate seal is lost. Re-application of the ciNPWT dressing/device within the intended therapy period is permitted and does not constitute 'intervention modification'. Data pertaining to dressing/device reapplication will be recorded. If an adequate seal cannot be achieved during the intended therapy period, discontinuation of the intervention is permitted and will be recorded.

8.5 Cessation of treatment/ Continuation of intervention after the trial

The double skin preparation with 2% alcoholic chlorhexidine followed by an alcoholic iodine solution intervention will only be applied in theatre prior to skin preparation.

Subcuticular continuous skin closure with an absorbable suture will only be applied intra-operatively.

Closed incision negative pressure wound therapy (ciNPWT) as a dressing applied in theatre is an intervention that should only be applied in theatre. Participants may return home with a device still in place on discharge from hospital. The length of device usage will be recorded for each participant but should be according to manufacturer's instructions (N.B. Smith& Nephew ciNPWT is a minimum of 7 days)2 hours as set out in Section 8.2.

It is recognised that there may be instances where a patient randomised to any arm within this pillar may experience wound complications in the post-operative period that the clinical team feel would be best managed by applying ciNPWT. The use of ciNPWT for this specific indication post-operatively is permitted within any arm in this pillar.

8.6 Intervention supply and storage

8.6.1 Intervention supplies

The interventions used within the ROSSINI-Platform trial are either supplied free of charge by the manufacturer of the intervention or they are obtained from standard hospital stock.

For those interventions supplied for free directly from the manufactureran initial supply of the interventions will be delivered to each site prior to site opening. The process for appropriate resupply and delivery arrangements will be explained during the Site Initiation Visit.

The provision of interventions for the LLA Pillar in the ROSSINI-Platform Trial are detailed below

Intervention 1: Double skin preparation with 2% alcoholic chlorhexidine followed by an alcoholic iodine solution

- No supplier required / not applicable – Standard hospital stock used

Intervention 2: Subcuticular continuous skin closure with an absorbable suture

- No supplier required / not applicable – Standard hospital stock used

Intervention 3: Closed incision negative pressure wound therapy (ciNPWT) as a dressing applied in theatre

- Industry partner
- Sites are permitted to use standard hospital stock

8.6.2 Packaging and labelling

There are no special packaging or labelling requirements for the interventions being used in the ROSSINI-Platform LLA Pillar.

Appropriate arrangements must be made to ensure availability of the intervention(s) when needed, while also ensuring that intervention(s) supplied for the trial are not used for non-trial indications. It is recommended that the trial interventions (or box in which they are held) be marked with a label "For ROSSINI-Platform Trial Use Only". The labels will be provided in the Investigator Site File (ISF) and are available from the ROSSINI-Platform Trial Office should sites require additional supplies.

8.6.3 Intervention storage

All interventions will be stored in a secure, clean, dry place free from damp at room temperature and within the supplied sterile packaging. No specific special requirements are required above the standard storage conditions of theatre products and refrigeration will not be necessary. Any excess intervention material will be disposed of in the hospital's standard clinical waste bins as per local hospital protocol. Interventions must only be used for patients within the trial, randomised to the arm in question. Any centres using those interventions supplied for free by the manufacturer outside of the trial setting may be cautioned, asked to withdraw from the trial or be asked for reimbursement.

8.6.4 Storage deviations

Not applicable. There are no special storage requirements for the interventions being provided free of charge via the ROSSINI-Platform trial office, and therefore we do not expect any storage deviation to occur

For any trial interventions that are from standard hospital stock, sites should follow local policies and Standard Operating Procedures (SOPs).

8.6.5 Intervention recalls

In the event that trial intervention(s) provided via the ROSSINI-Platform Trial Office directly to participating sites, is recalled by the manufacturer, the ROSSINI-Platform Trial Office will promptly notify all participating sites and hospitals of the recall. The notification will include details of the recall, including the reason, the specific intervention batches affected (if these details have been provided by the manufacturer) and any immediate actions required (i.e. cease the use of the recalled intervention immediately, quarantine any remaining stock of the recalled intervention to prevent further use.

For any interventions not supplied via the ROSSINI-Platform Trial Office i.e. where the intervention is taken from standard hospital stock, sites should follow usual Trust procedures / recall SOPs for any intervention recalls.

8.7 Accountability

Each individual recruiting site shall be responsible for ensuring adequate stock of interventions prior to randomisation of patients into the trial.

Each site must ensure that stock levels are adequate prior to randomisation to avoid protocol deviations.

9. PILLAR SPECIFIC ADVERSE EVENT REPORTING

Within the ROSSINI-Platform trial there are adverse events which are either:

1. Common to all pillars within the platform
2. Pillar-specific

The Master Protocol describes the process for adverse event reporting within the ROSSINI-Platform. This includes a description of:

- The reporting period for ALL safety events within the ROSSINI-Platform

- The process for reporting of ALL safety events within the ROSSINI-Platform
- Serious Adverse Events (SAEs) common to all pillars requiring expedited reporting within the ROSSINI-Platform
- SAEs common to all pillars requiring non-expedited reporting within the ROSSINI-Platform

Please refer to the Master Protocol for the process for safety reporting which must be followed.

9.1 Pillar-Specific Serious Adverse Events requiring non-expedited reporting to the Trial Office

Within this pillar, the expected intervention-specific adverse events are:

- Intolerance or pain whilst the ciNPWT device is in use
- Blistering of skin or tearing of the skin due to the adhesive dressings used to achieve a seal for ciNPWT

These events require non-expedited reporting and should be reported on the In-Theatre eCRF or the Day of Discharge eCRF.

Events subject to non-expedited reporting and should be reported according to the process detailed in Section 11.5.2 of the Master Protocol.

10. REFERENCE LIST

1. Al-Saadi, N., Al-Hashimi, K., Popplewell, M., Fabre, I., Gwilym, B. L., Hitchman, L., Chetter, I., Bosanquet, D. C., & Wall, M. L. (2024). The incidence of surgical site infection following major lower limb amputation: A systematic review. International Wound Journal, 21(7), e14946. https://doi.org/10.1111/IWJ.14946
2. Souroullas, P., Barnes, R., Carradice, D., Smith, G., Huang, C., & Chetter, I. (2022). Extended-course antibiotic prophylaxis in lower limb amputation: randomized clinical trial. The British Journal of Surgery, 109(5), 426–432. https://doi.org/10.1093/BJS/ZNAC053
3. Dillingham, T. R., Pezzin, L. E., & Shore, A. D. (2005). Reamputation, mortality, and health care costs among persons with dysvascular lower-limb amputations. Archives of Physical Medicine and Rehabilitation, 86(3), 480–486. https://doi.org/10.1016/j.apmr.2004.06.072
4. Torbjörnsson, E., Ottosson, C., Boström, L., Blomgren, L., Malmstedt, J., & Fagerdahl, A. M. (2022). Health-related quality of life and prosthesis use among patients amputated due to peripheral arterial disease–a one-year follow-up. Disability and Rehabilitation, 44(10), 2149–2157. https://doi.org/10.1080/09638288.2020.1824025
5. Turner, A. P., Meites, T. M., Williams, R. M., Henderson, A. W., Norvell, D. C., Hakimi, K. N., & Czerniecki, J. M. (2015). Suicidal Ideation among Individuals with Dysvascular Lower Extremity Amputation. Archives of Physical Medicine and Rehabilitation, 96(8), 1404–1410. https://doi.org/10.1016/j.apmr.2015.04.001
6. Morrison, T. N., Chen, A. F., Taneja, M., Küçükdurmaz, F., Rothman, R. H., & Parvizi, J. (2016). Single vs Repeat Surgical Skin Preparations for Reducing Surgical Site Infection After Total Joint Arthroplasty: A Prospective, Randomized, Double-Blinded Study. The Journal of Arthroplasty, 31(6), 1289–1294. https://doi.org/10.1016/J.ARTH.2015.12.009
7. Davies BM, Patel HC. Systematic Review and Meta-Analysis of Preoperative Antisepsis with Combination Chlorhexidine and Povidone-Iodine. Surg J (N Y). 2016 Aug 10;2(3):e70-e77. doi: 10.1055/s-0036-1587691.
8. Jolivet, S., & Lucet, J. C. (2019). Surgical field and skin preparation. Orthopaedics & Traumatology: Surgery & Research, 105(1), S1–S6. https://doi.org/10.1016/J.OTSR.2018.04.033
9. Gurusamy, K. S., Toon, C. D., Allen, V. B., & Davidson, B. R. (2014). Continuous versus interrupted skin sutures for non-obstetric surgery. Cochrane Database of Systematic Reviews, 2014(2). https://doi.org/10.1002/14651858.CD010365.PUB2/MEDIA/CDSR/CD010365/IMAGE_N/NCD010365-CMP-001-06.PNG
10. Coulston, J. E., Tuff, V., Twine, C. P., Chester, J. F., Eyers, P. S., & Stewart, A. H. R. (2012). Surgical factors in the prevention of infection following major lower limb

amputation. European Journal of Vascular and Endovascular Surgery, 43(5), 556–560. https://doi.org/10.1016/j.ejvs.2012.01.029

11. Gwilym, B. L., Bosanquet, D. C., Dovell, G., Ambler, G. K., Dattani, N., Shalhoub, J., Onida, S., Forsythe, R. O., Benson, R. A., Nandhra, S., Preece, R., Hitchman, L., Coughlin, P., & Saratzis Brenig L.; ORCID: http://orcid.org/0000-0002-5403-8720 AO - Ambler, Graeme K.; ORCID: http://orcid.org/0000-0002-3024-6365 AO - Nandhra, Sandip; ORCID: http://orcid.org/0000-0002-6036-5760, A. A. O.-G. (2021). Editor's Choice - Systematic Review and Meta-Analysis of Wound Adjuncts for the Prevention of Groin Wound Surgical Site Infection in Arterial Surgery. European Journal of Vascular and Endovascular Surgery, 61(4), 636–646. https://doi.org/http://dx.doi.org/10.1016/j.ejvs.2020.11.053

1. 11. Frodl, A., Geisteuer, N., Fuchs, A., Nymark, T., & Schmal, H. (2022). Incisional negative pressure wound therapy to reduce surgical-site infections in major limb amputations: a meta-analysis. EFORT Open Reviews, 7(8), 526–532. https://doi.org/10.1530/EOR-22-0049

11. APPENDIX