ROSSINI-PLATFORM TRIAL

MASTER PROTOCOL

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

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:**
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Funding scheme	NIHR Health Technology Assessment (HTA) Programme
Funder's reference number	NIHR163832

The funder of the trial has had no role in the trial design, and will have no role in the data collection, data analysis or data interpretation, or in the writing of the final report; and the decision to submit the report for publication. This project is funded by the NIHR HTA Programme.

The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

SUPPLIERS	
Smith and Nephew	Provision of intervention
ESSITY	Provision of intervention
SERB	Provision of intervention
MÖLNLYCKE	Provision of intervention

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, 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
Protocol version number:	Version: __ __
Protocol version date:	__ __ /__ __ __ /__ __ __ __
CI name:	
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 ROSSINI-Platform trial only. The protocol should not be used as a guide for the treatment of patients not taking part in 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, 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), 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:	
Protocol version number:	Version: __ __
Protocol version date:	__ __ /__ __ __ /__ __ __ __
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Name of Site:	
Signature and date:	_____ __ __ /__ __ __ /__ __ __ __

ADMINISTRATIVE INFORMATION

Reference Numbers	
EudraCT number	< EudraCT number >
Sponsor number	< Sponsor number >
ISRCTN reference number	< ISRCTN reference number >
IRAS reference number	1009318

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Abbreviation	Term
AE	Adverse Event
AHP	Allied Health Professional
AR	Adverse Reaction
ARR	Absolute Risk Reduction
API	Associate Principal Investigator
BCTU	Birmingham Clinical Trials Unit
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDWH	Central Digital Wound Hub
CEAC	Cost Effectiveness Acceptability Curves
CI	Chief Investigator
CQUIN	Commissioning for Quality and Innovation
CRC	Concurrently Randomised Cohort
DCF	Data Clarification Form
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DSA	Data Sharing Agreement
DSP	Digital Signal Processing
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
ETC	Excess Treatment Cost
ETMG	Executive Trial Management Group
GCP	Good Clinical Practice
GSTT	Guys and St Thomas' NHS Foundation Trust

HEAP	Health Economics Analysis Plan
HRA	Health Research Authority
HSCN	Health and Social Care Network
HTA	Health Technology Assessment
HTTPS	Hypertext Transfer Protocol Secure
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IRAS	Integrated Research Application System
LLA	Lower Limb Amputation
MAMS	Multi-Arm Multi-Stage
MHRA	Medicines and Healthcare Products Regulatory Agency
MRC CTU	Medical Research Council Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PI	Principal Investigator
PICO	Population, Intervention, Comparator, Outcome
PIS	Patient Information Sheet
POMR	Postperative Mortality Rate
PPI	Public and Patient Involvement
PPIE	Patient and Public Involvement and Engagement
PROMs	Patient Reported Outcome Measures
PSP	Pillar Specific Protocol
QALY	Quality Adjusted Life Year

QoL	Quality of Life
RCT	Randomised Control Trial
RDN	NIHR Research Delivery Network
REC	Research Ethics Committee
RGT	University of Birmingham Research Governance Team
RUQ	Resource Use Questionnaire
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SSI	Surgical Site Infection
SUSAR	Suspected Unexpected serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UCL-MRC	University College London – Medical Research Council
UK	United Kingdom
UoB	University of Birmingham

TRIAL SUMMARY

Title

The ROSSINI-Platform Trial: A basket factorial multi-arm multi-stage (MAMS) platform randomised controlled trial (RCT) to evaluate the use of multiple interventions to reduce surgical site infection (SSI) across several types of surgery.

Primary Objective

To determine whether several specific peri-operative interventions result in decreased risks of SSI, up to 30 days postoperatively, in patients undergoing surgery across different surgical specialties including: 'vascular groin', lower limb amputation (LLA), breast, cardiac surgery, obstetrics and neurosurgery.

Trial design

A multi-speciality 'Basket Factorial MAMS' platform trial, in which multiple phase III factorial MAMS RCTs will be run in parallel within different surgical cohorts ('pillars'), under one overall master protocol and governance structure. Individual trials in each pillar are pragmatic, MAMS 2x2x2 factorial RCTs with blinded assessment of outcomes. Internal pilot phases are planned at platform, pillar and intervention levels.

Participant population and sample size

Adults undergoing surgery in any of the following surgical specialties or 'pillars': vascular groin, LLA, breast, cardiac surgery, or patients over 12 years in obstetrics and neurosurgery.

Sample sizes have been calculated across each pillar based on evidenced risks of SSI in the control arm and prespecified cross-pillar absolute risk reduction (ARR) strategy. Maximum sample sizes for each pillar are:

	Vascular - Groin	LLA	Obstetric	Breast	Neuro-surgery	Cardiac Surgery
Baseline SSI rate	17.5%	21%	8%	5%	5%	4.5%
Interventional arm SSI rate	13.5%	16%	6%	3%	3%	2.5%
Absolute Risk Reduction	4%	5%	2%	2%	2%	2%
Overall sample size needed	3,648	2,686	7,266	4,280	4,280	3,764

The maximum sample size combined across all pillars is 25,924 patients

Setting

Around 100 NHS hospitals across the UK across multiple specialties.

Eligibility criteria

Platform-level eligibility:

- Patients undergoing vascular groin, LLA, breast, cardiac surgery, obstetrics or neurosurgery at a ROSSINI-Platform participating hospital.
- Patients with an email address and/or telephone number who are able and willing to provide follow-up through the Central Digital Wound Hub (CDWH)*

Pillar-level eligibility:

Each pillar has pillar-specific eligibility criteria as detailed in individual Pillar Specific Protocols (PSP).

Interventions

Individual pillars have prioritised three specific peri-operative interventions for initial testing based on: (1) evidence of potential clinical effectiveness, (2) patient acceptability and (3) clinician equipoise within their clinical area. Each individual intervention will be compared against those participants not allocated to receive the intervention (e.g. A vs not A).

Outcome measures

Primary Outcome:

SSI within 30 days of surgery according to the modified Centers for Disease Control (CDC) criteria, assessed by local research teams at hospital discharge and then remotely through the CDWH augmented by patient questionnaires and wound photographs collected weekly via a patient-facing App.

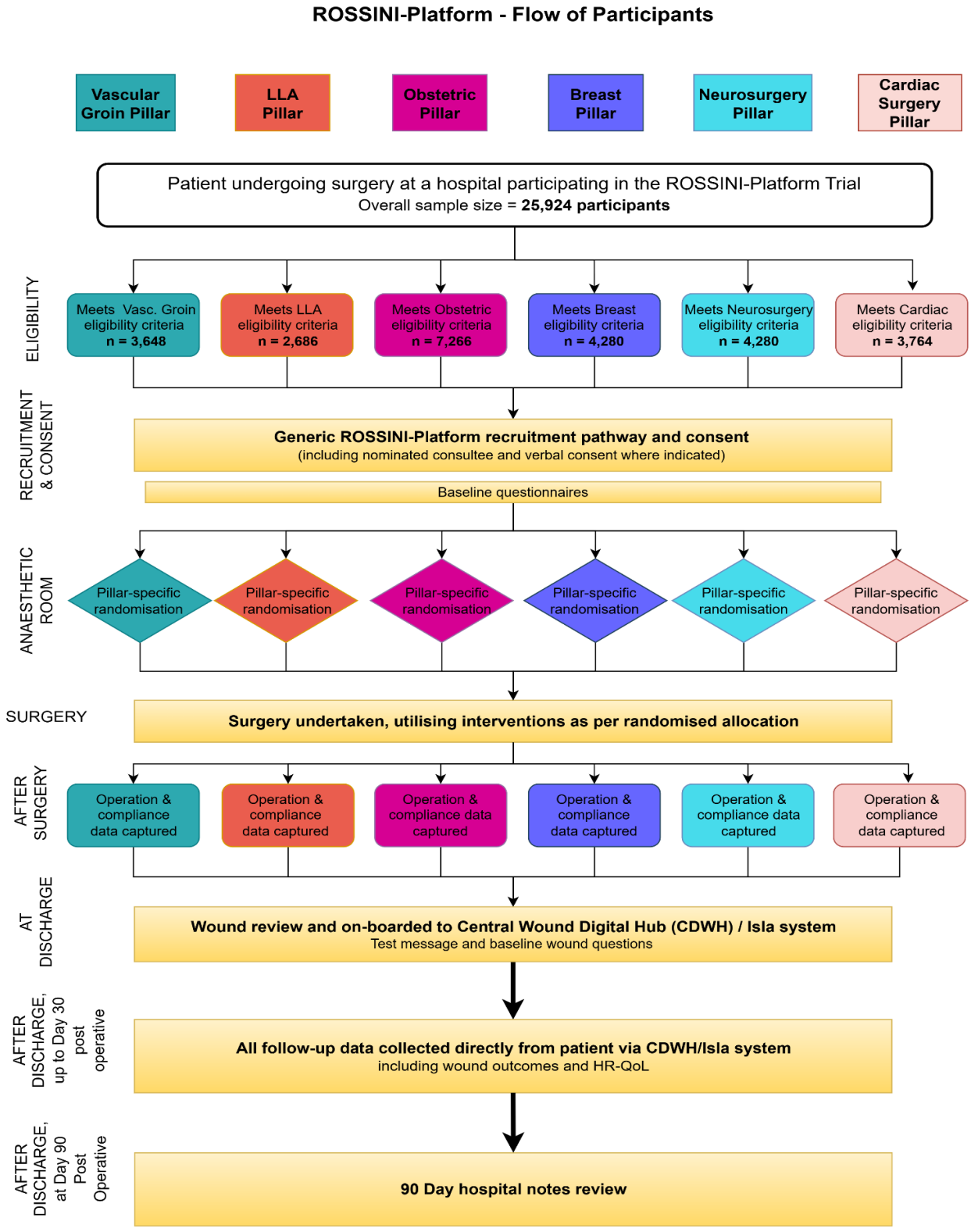
Secondary Outcomes:

- 30-day and 90-day postoperative mortality rate (POMR).
- 30-day postoperative worst wound complication (Clavien-Dindo or / Landriel-Ibanez classification).
- Risk of wound-related or intervention-related Serious Adverse Events up to 30 and 90 days post-surgery.
- Length of hospital stay after surgery as measured from the date of surgery to the date fit for discharge collected via hospital records.

- Risk of hospital re-admission for wound related complications within 30 and 90 days post-discharge.
- Risk of wound reopening and/or re-operations within 30 and 90 days post-surgery.
- Preference-based Quality of Life (QoL EQ-5D-5L) at Baseline, Day of Discharge and weekly until Day 30 post-surgery via Isla.
- Cost effectiveness (Resource Use Questionnaire; RUQ)

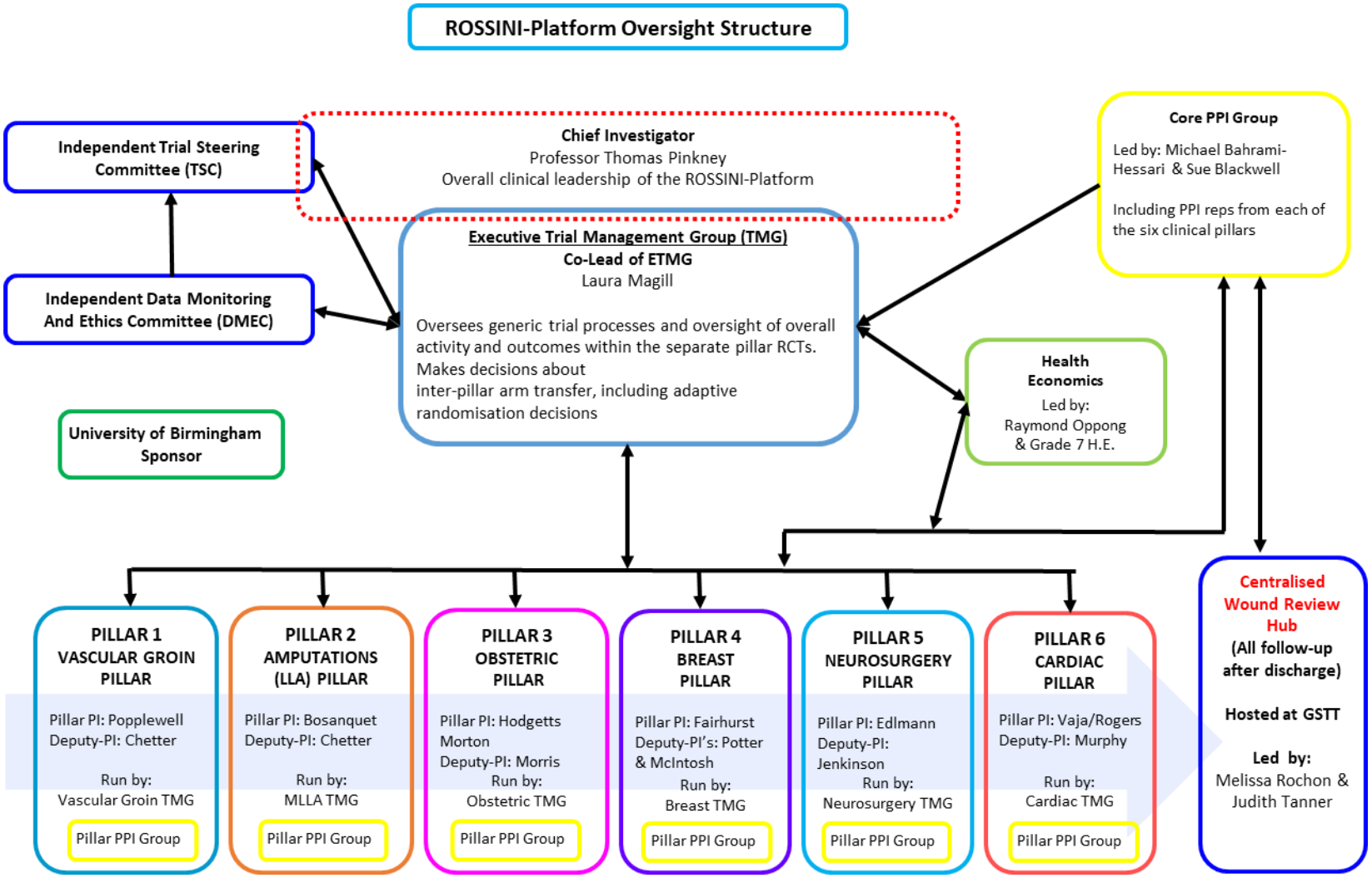
TRIAL SCHEMA

Figure 1.0



TRIAL GOVERNANCE STRUCTURE

Figure 2.0



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1. PROTOCOL STRUCTURE

The structure of this protocol is different to that used for a conventional trial 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/arms or 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 a Master Protocol (overview and design features of the study) and multiple Pillar-Specific Protocols (PSP) (including details of all interventions currently being studied in each Pillar).

Master Protocol

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 has the following structure:

- The background and rationale for studying surgical site infection (SSI).
- The background and rationale for the research approach
- The trial design including study setting, the criteria that define eligibility for the ROSSINI-Platform, treatment allocation, principles of application of trial interventions, trial outcomes, methods to control bias, principles of the statistical analysis, and criteria for termination of the trial
- The trial conduct including recruitment methods, data collection, data management, and management of participant safety
- The overall trial governance structures including patient and public involvement and engagement (PPIE) and ethical and regulatory considerations.

Pillar-Specific Protocols

PSPs will contain all information about the interventions that will be the subject of the ROSSINI-Platform, within that Pillar. As such, the Master Protocol does not include information about the intervention(s) that will be evaluated within the ROSSINI-Platform but rather provides the framework on which multiple different interventions, within pillars, can exist within this trial. Each new intervention or addition of pillars will be submitted for regulatory approval prior to commencement. It is anticipated that the PSPs will change over time with the removal and addition of interventions, as well as removal and addition of entire pillars. Each PSP has the following structure:

- Background on the patient population and interventions within that pillar
- Criteria that determine eligibility of patients to that pillar
- The features of the interventions and how they are delivered

- Any outcomes and data collection that are specific to the pillar and additional to those specified in the Master Protocol
- Any ethical, consent and safety issues specific to the pillar
- The organisation of management of the pillar

2. BACKGROUND AND RATIONALE

At the end of February 2024, there were over 7.6 million patients waiting for planned hospital treatment within the NHS - the majority of which were elective surgical operations[1]. The rising backlog and ongoing pressures on both elective and emergency surgical services mean there has never been a more important time for preventable postoperative complications to be avoided. Surgical Site Infection (SSI) is now the most common healthcare-associated infection, overtaking others such as MRSA, Clostridium difficile, hospital-acquired pneumonia and catheter-associated infections after significant and sustained investment in these other areas over recent years[2]. With over 4 million operations in the UK, there are at least a quarter of a million patients affected annually[3-5]. At an average cost of £3,500 per SSI, it is estimated that SSIs currently cost the NHS over £700 million per year[6,7]. In addition to this financial burden of SSI caused by prolonged postoperative hospital stay and additional inpatient/outpatient treatment costs, there is significant association between the development of an SSI and morbidity and mortality rates[8]. Patients with an SSI are twice as likely to die as those without an SSI, and around one third of postoperative deaths are attributable, at least in part, to SSI[9].

It is well established that SSI incidence has been underreported for many years and traditional monitoring relies heavily on passive surveillance with little post-discharge review. At least 60% of SSIs present in the community post-discharge and are often unaccounted for[10]. With the increase of enhanced recovery programmes and shorter lengths of hospital stay, the proportion of SSIs presenting outside of hospital has increased further over recent years[11], and a high-quality post-discharge assessment process is recognised as a fundamental quality marker in SSI research[12,13]. The detrimental impact of SSIs has been the subject of heightened interest over the past decade, and were the subject of a recent National Institute for Health and Care Excellence (NICE) quality standard[14]. This document described SSI as a high-priority area for quality improvement and suggests that commissioners may wish to adopt SSI rates as a CQUIN (Commissioning for QUality and INnovation) target[15]. It is therefore likely to remain an area of significant and sustained interest for patients, clinicians and health care providers in the coming decade.

2.1 Trial rationale – the need for a multi-specialty platform trial in SSI reduction

Preventing SSI is complex and requires interventions throughout the surgical care pathway. SSIs are often caused by wound contamination by endogenous bacteria that can originate from the patient's skin, mucous membranes or hollow viscera[16,17]. This has resulted in the development of intraoperative interventions targeted at different pathoaetiologies of SSI to try to decrease this contamination and thereby decrease SSI rates. Unfortunately, clinical studies exploring the efficacy

of many of these interventions have often been underpowered or poorly designed, leaving uncertainty if they are clinically and cost-effective. A key shortcoming of all current national and international guidelines on the reduction of SSI is their highly generic nature; the recommendations apply to all types of surgery and are not specialty-specific or surgical site/target organ-specific[18-20]. This is largely a result of a small number of high-quality trials making up the evidence base[21], meaning that research findings from one surgical indication are inevitably extrapolated to other settings. This can lead to both over-promotion of interventions which have shown clinical effectiveness within a discrete area of surgery, and the discarding of others which might confer benefit when used in a different setting. Sometimes recommendations are made based on the contamination level of the wound. This primary classification system for wounds by contamination (clean; clean-contaminated; contaminated and dirty) has been in place since 1964 [22]. Whilst it can be useful to demonstrate the range of operation types and subsequent highly variable risk of SSI from <2% to >40%, it is overly simplistic. Within this system, an elective wrist operation, an open abdominal aortic aneurysm repair and a leg amputation are all grouped together as 'clean' operations. Similarly, elective operations for both lung cancer and rectal cancer can be 'clean-contaminated'. This is counter intuitive as whilst the aetiology of SSI is multifactorial, mechanisms of development of SSI, including the source and nature of pathogenic organisms responsible, are not the same across the body. Further work across different surgical operation types, including more granular testing of SSI prevention measures, would allow evidence-driven stratification according to the specific procedure a patient is undergoing. This would confer significant benefit for both patients and the health service due to a reduction in SSI rates across the entirety of surgery.

2.2 Justification for participant population – choice of pillar specialties

The six surgical specialties ('pillars') included in the initial phase of the platform were selected as those with a suitable baseline SSI event rate and evidence of a significant detrimental impact from SSI on their patients, often including identification of SSI as an unmet research need in priority setting partnerships. These clinical groups have a proven track record in clinical research and access to an established and active research delivery network.

Other surgical specialty groups are interested in becoming involved in the platform after this initial phase. During the course of the trial, we will develop robust and transparent criteria for adding new pillars to the platform, whilst recognising that such additional pillars would require further funding.

2.3 Justification for the trial design – choice of pillar specialties

2.3.1 Multi-arm, Multi-stage (MAMS) Trials in Surgery

It is increasingly recognised that a single 'magic bullet' to prevent SSI does not exist; rather a cumulative package of measures for a particular operation type or surgical setting are likely to be most effective[20]. However, 'bundle' trials often fail to change clinical practice as it is not possible to reliably measure the effectiveness (or potential harm) of individual components; for this, direct intervention-level comparisons are required. Some years ago, our group recognised that research into SSI prevention lends itself well to MAMS trial designs, with adaptive randomisation strategies

also possible, because the primary outcome result is, by definition, available 30 days after the operation/intervention. The MAMS design allows multiple individual interventions to be evaluated simultaneously, and the simultaneous nature of the multi-arm and multi-stage assessment renders it highly efficient both in terms of speed and cost. The methodology was proven to be highly successful in the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) suite of trials in prostate cancer[23-26], but had not been used in a surgical context. We established a collaboration with the pioneers of the MAMS design, Professor Parmar and his team at the Medical Research Council Clinical Trials Unit (MRC CTU), to design the National Institute for Health and Care Research (NIHR) funded ROSSINI 2 trial.

2.3.2 The ROSSINI2 Trial

ROSSINI 2 is a separate ongoing major multicentre randomised controlled trial (RCT) exploring the effectiveness of three intraoperative interventions for the reduction of SSI in patients undergoing abdominal surgery only, utilising a MAMS selection design[27-29]. ROSSINI 2 was funded by the NIHR Heath Technology Assessment (HTA) programme in 2018 and commenced recruitment in March 2019. Two within-trial interim analyses have been undertaken and six ineffective arms dropped from an original eight arms. We have shown that it is possible to decrease both the time and cost investment necessary to simultaneously determine if several non-bundled interventions are effective in reducing SSI rates, and that MAMS RCTs can be delivered in a modern surgical context. In late April 2024, the original iteration of ROSSINI 2 completed recruitment, with 5,334 patients recruited from 52 sites across the United Kingdom (UK). The trial has now rolled seamlessly into a discrete platform trial (which was always an option) with a new costed extension phase to allow the recruitment of a further 4,269 patients to establish the clinical and cost effectiveness of two completely new interventions in this population. Whilst ROSSINI 2 will continue to deliver robust information on interventions to reduce SSI in **abdominal surgery**, findings will not be translatable into other types of surgery where mechanisms of SSI, including pathogenic organisms and patient risk profiles differ.

2.3.3 The ROSSINI-Platform Trial

This new platform trial will build upon and extend the principles established in ROSSINI 2 across a variety of different surgical settings. Preliminary work for this platform was funded by an NIHR HTA platform accelerator award [NIHR156728]. The platform trial will utilise bespoke 'Basket factorial MAMS' methodology in which multiple full-scale factorial MAMS RCTs will be run in parallel within different surgical cohorts ('pillars'), organised by wound type/site, under one overarching protocol and governance structure. These trials will simultaneously assess the effectiveness of multiple carefully-selected interventions alone or in combination – and crucially will share learning between pillars to take effective arms (individual interventions or combination. Whilst there are no formal analyses planned between pillars, knowledge gained from one pillar may be used to help guide

future intervention choice within other pillars. This will provide robust and context-specific evidence in a highly efficient manner both in terms of time and cost.

2.4 Justification for choice of interventions

Pillar teams were asked to select interventions which are applied in the peri-operative setting and could be randomised at an individual patient level. Literature reviews were also undertaken to identify interventions which had the most credible chance of being effective in each pillar, as supported by current evidence. The interventions had to not be in widespread current routine use, and surgeons must have reported equipoise to accept randomisation to use (and not use) them during their operations. Patient acceptability review was also mandated. If pillars had multiple options of interventions which could be investigated, it was agreed that priority would be given to those which had the potential to also be applied in other clinical settings if found to be effective, as part of our plan to move successful interventions between pillars for further testing within the lifetime of the trial.

Specific details of the individual pillar interventions, their justification and use within pillars is detailed in each PSP.

2.5 Justification of assessment method for primary outcome

A recurring challenge in the delivery of high-quality SSI research is the delivery of accurate, reproducible and blinded wound assessments for the determination of the primary outcome. With >60% of SSIs occurring after discharge, the previous gold standard has been to bring all patients back to hospital for a face-to-face wound assessment and review at around 30 days after surgery. This is expensive, increasingly challenging in the post-pandemic National Health Service (NHS), not environmentally efficient and would simply not be deliverable in a trial of >25,000 patients. It also risks missing minor SSI events which resolve before a single 30-day assessment. The ROSSINI-Platform will therefore utilise a ‘gold standard PLUS’ approach by using telemedicine, validated tools for remote SSI diagnosis, and pre-existing infrastructure and dedicated expertise within a Central Digital Wound Hub (CDWH) at Guy’s and St Thomas’ NHS Foundation Trust for all post-discharge patient-level follow-up.

2.6 Isla and the CDWH

The CDHW employs image-based remote wound technology provided by the Isla platform[30]. After competitive tender, the Royal Brompton and Harefield hospitals (part of GSTT) commissioned Isla to develop an image and questionnaire digital SSI platform using patient-connected devices. The "Tracking Wound Infection with Smartphone Technology" (TWIST) RCT used a similar combination of images and a questionnaire to proactively diagnose SSI with a sensitivity of 100% and specificity of 93.6% (95% CI: 90.9–96.2%)[31]. This trial demonstrated the feasibility, safety, and clinical efficacy of remote postoperative wound monitoring. The TWIST team subsequently conducted a single-arm pilot implementation study of remote digital postoperative wound monitoring across two tertiary

care hospitals in the UK, using Isla. The quality of the Isla interface, ease of use and patient satisfaction were all rated very highly[32].

3. AIMS AND OBJECTIVES

ROSSINI-Platform is a multi-speciality 'Basket Factorial MAMS' platform trial, of multiple phase III factorial MAMS RCTs within different surgical specialties ('pillars') with a 3-month internal pilot phase at platform, pillar and arm levels. The aim of ROSSINI-Platform is to investigate the clinical and cost effectiveness of several peri-operative interventions in reducing SSI rates in patients undergoing surgery across six specialties: vascular groin, LLA, breast, cardiac surgery, obstetrics and neurosurgery.

The overarching research question (PICO) for the ROSSINI-Platform trial is:

Population: Patients undergoing surgical procedures within six separate surgical specialties or 'pillars' (vascular groin, LLA, breast, cardiac, obstetrics or neurosurgery).

Intervention: Three specific peri-operative interventions, selected individually for each clinical pillar, used alone or in combination.

Comparator: Standard care.

Outcome: Surgical site infection within 30 days of surgery as defined by the modified Centers for Disease Control and Prevention (CDC); evaluated at discharge and then through a blinded centralised Wound Assessment Hub after discharge until 30 days post-surgery.

The aims and objectives for the pilot and main trial are defined below.

3.1 Internal pilot objectives

The ROSSINI-Platform trial includes a 3-month pilot phase with feasibility assessed at platform, pillar and intervention levels which will inform decisions on progression of the platform.

The Master protocol details the PLATFORM level objectives and outcomes only.

Pillar and intervention level objectives and outcomes are detailed within each PSP.

The aims of the internal pilot are to assess:

At PLATFORM Level:

- Number of sites opened
- Number of participants recruited
- Participant engagement with the CDWH

Section 9 details the criteria that will determine the continuation of the platform beyond the end of the pilot.

At PILLAR Level:

- Number of sites opened
- Number of participants recruited
- Completion of follow-up data at the CDWH
- Completion of participant-level data at BCTU

At INTERVENTION Level:

- Compliance with the randomised allocation by operating surgeon
- Relative level of acceptance by the clinician of the randomisation of each intervention in proportion to the other interventions in that pillar.

3.2 Main trial objectives

3.2.1 Clinical aims and objectives

Primary Objective:

The primary objective is to determine if specific peri-operative interventions, used alone or in combination, result in decreased risks of SSI within 30-days post-surgery in patients undergoing surgery across six surgical specialties: vascular groin, LLA, breast, cardiac, obstetrics, and neurosurgery.

Secondary Objectives:

Do the peri-operative interventions:

- Improve quality of life (QoL) up to 30 days post-surgery?
- Reduce the rate of mortality up to 90-days post-surgery?
- Reduce the risks of wound complications up to 30 days post-surgery?
- Have an acceptable safety profile?
- Reduce the length of stay in hospital?
- Reduce the risk of wound complication related hospital re-admissions within 30 and 90 days post-surgery?
- Reduce the risk of wound reopening and/ or re-operations within 90 days post-surgery?

Exploratory Objectives:

Is there a difference in intervention effect depending on participant co-morbidities (e.g. diabetes, smoking, body mass index (BMI)), duration of operation and operative technique used?

3.2.2 Economic aims and objectives

The health economic evaluation will assess the cost-effectiveness of the compared interventions from an NHS and personal services perspective for patients undergoing surgery in each of the pillars.

4. TRIAL DESIGN AND SETTING

4.1 Trial design

The ROSSINI-Platform is a multi-speciality 'Basket Factorial MAMS' platform trial, in which multiple phase III factorial MAMS RCTs are run in parallel within different surgical cohorts ('pillars').

The trial in each pillar is a pragmatic, MAMS 2x2x2 factorial trial with blinded outcome assessment. The trial includes a 3-month internal pilot phase with feasibility assessed at platform, pillar and intervention level, plus an economic evaluation. Participants within each pillar will be randomised to one of the eight combinations of three interventions to be used during the same operation, via seven possible treatment arms plus one control arm.

See **Figure 1** ROSSINI-Platform Trial Schema.

4.2 Trial setting

Approximately 100 NHS hospitals throughout the UK.

Any NHS hospital undertaking at least one of the pillar operation types is eligible to participate in the platform. Hospitals which perform the rarer pillar operation types, i.e., the 32 neurosurgery units and the 34 cardiac surgery units, and those that plan to enter patients across multiple pillars will be prioritised. Hospital sites will initially open for the overall platform trial and subsequently select which clinical pillars to participate in based on capability assessments, local interest and equipoise. Sites will be encouraged and supported to participate in multiple pillars.

The individual RCTs within each pillar will be conducted by separate teams of specialist surgeons and surgical collaborative research groups supported by members of the central delivery team.

4.3 Site Principal Investigator (PI) and Site Pillar Lead

Each hospital site that participates in the ROSSINI-Platform, must identify an appropriate Local Principal Investigator (PI) authorised by the site and ethics committee to lead and coordinate the work of the platform on behalf of the site. For the purposes of regulatory and ethics applications and approvals, only one PI should be named per hospital site.

Hospital sites are encouraged to participate in multiple pillars. Each pillar will require a named Pillar Lead, who will have the relevant clinical expertise for the pillar. The local site PI may also be a Site Pillar Lead. Site Pillar Leads can also appoint a Deputy Site Pillar Lead if required.

The Site Pillar Leads will work alongside the PI at the trial site, and they may undertake part or all of the local PIs activities for a specific pillar. The PI must ensure these individuals are adequately

qualified by education, training, and experience to assume responsibility for the proper conduct of the pillar-specific trial at their site. This delegation of duties will be documented via the ROSSINI-Platform Site PI to Site Pillar Lead Delegation of Duties log. Each Site Pillar Lead will also sign a Site Pillar Lead Investigator declaration to formally acknowledge their roles and responsibilities at the site. This declaration ensures that the Site Pillar Lead is aware and agrees to the terms of the study, including compliance with the protocol and regulatory and ethical standards.

4.4 Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation:

Type A = No higher than the risk of standard medical care

The interventions being assessed in the trial are already being used by a small number of surgeons nationally and internationally. They are all commercially available and approved for use in the UK. In the absence of level 1 evidence, current behaviours for SSI reduction practice are influenced by surgeon experience and hospital policies governing local availability. As a pragmatic trial, ROSSINI-Platform is designed to have minimal impact upon a patient's standard clinical care and thereby enhance recruitment and adherence to arm allocation, whilst maximising follow-up rates. We propose to randomise patients to receive adjunctive interventions in addition to standard care in an attempt to decrease their likelihood of developing a potentially serious postoperative complication. None of the interventions are known to cause harm and none will significantly increase the time of an operation or make it more technically difficult.

5. ELIGIBILITY

Within this Master Protocol, the eligibility criteria applicable to all potential participants is defined.

Specific eligibility criteria for each Pillar are listed in the individual PSP.

Potential participants must meet the eligibility within the Master protocol and the eligibility within the appropriate PSP to be eligible for randomisation.

Eligibility within all pillars will be confirmed by medically qualified doctors.

5.1 Inclusion criteria

- Patients undergoing vascular groin, LLA, breast, cardiac, obstetric, or neurosurgery at a ROSSINI-Platform participating hospital.
- Patients (or via support from family member/ carer etc) with an email address and/or telephone number who are able and willing to provide follow-up through the CDWH*

- Able to give informed consent, with interpreters where necessary OR representative provides assent/consent if a patient temporarily lacks capacity.

5.2 Exclusion criteria

Previous participation in any Pillar of the ROSSINI-Platform within the last 90 days.

5.3 Co-enrolment

Co-enrolment into all other clinical studies (including observational studies and RCTs) will be considered on a case-by-case basis by the Pillar level TMG. Prior to co-enrolment being agreed, the following will be reviewed and considered: study design and statistical considerations; legal and ethical considerations; biological and scientific rationale; patient considerations and logistical and organisational issues. This will ensure careful consideration of patient burden, compatibility of interventions, organisational issues and follow-up.

Co-enrolment to CTIMPs will be restricted to Type A trials that are comparable to the risk of standard medical care, where the IMP intervention(s) would commonly be used in the treatment of the patient, and where no biological interactions or additional safety reporting will be required for concomitant administration of the IMPs.

In pillars where patients will be recruited into the trial from an emergency care setting the research team at the site is highly unlikely to be aware if a participant is already participating in a clinical trial. Where a participant is subsequently found to have been participating in a concurrent trial, the site should inform the ROSSINI-Platform Trial Office, who will in turn request that the relevant Pillar lead assesses any safety concern or impact on the trial data. The site should follow its local procedure for reporting trial co-enrolment.

For co-enrolment to occur, an agreement will be reached between the respective trials team prior to the patient being considered for inclusion. A log of all patients co-enrolled will be maintained by the ROSSINI-Platform Trial Office.

A co-enrolment log which lists trials in which patients can be co-enrolled can be found on the ROSSINI-Platform website or is available from the ROSSINI-Platform Trial Office.

Should sites wish to co-enrol patients into ROSSINI-Platform and another study not listed on the co-enrolment log, sites **must** contact the ROSSINI-Platform Trial Office to discuss co-enrolment prior to enrolment into ROSSINI-Platform.

Details of the co-enrolment policy by Pillar are found within each PSP.

6. CONSENT CONSIDERATIONS

Most patients undergoing vascular groin, LLA, breast, cardiac, obstetric or neurosurgery as part of the ROSSINI-Platform will be able to provide fully informed consent. There are, however, some patients who meet the inclusion criteria for a pillar within the platform who are either unable to provide fully informed consent or are not able to consent at all due to a temporary impairment resulting from the indication for their surgery.

The methods of gaining consent for inclusion in the study differ between patients who are able to provide consent and those who are not.

The law around recruitment of patients who lack capacity is governed by the Medicines for Human Use (Clinical Trials) Regulations 2004, which apply to CTIMP research across the UK. These regulations set out specific provisions for including adults who lack capacity, including the requirement for consent to be provided by a legal representative (personal or professional). In England and Northern Ireland, the Mental Capacity Act 2005 (England) and the Mental Capacity Act (Northern Ireland) 2016 does not apply to CTIMPs but informs best practice in assessing capacity and safeguarding participants. In Scotland, the inclusion of adults lacking capacity is governed by both the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Adults with Incapacity (Scotland) Act 2000, which provides additional legal provisions for proxy decision-making and participant protection.

A legal representative can be asked to give consent on behalf of an adult lacking capacity to do so themselves.

Those who are able to act as a legal representative in Clinical Trials of Investigational Medicinal Products (CTIMPs), in England and Wales are:

- Personal legal representative i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult, and is available and willing to do so. If one is not available:
- Professional legal representative i.e. a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider.

Those who are able to act as a legal representative in Clinical Trials of Investigational Medicinal Products (CTIMPs), in Scotland are:

- Personal legal representative i.e.
    - Adult's Welfare Guardian or Welfare Attorney if not appointed
    - The adult's nearest relative, if neither are reasonably contactable
- Professional legal representative i.e. a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider.

See Appendix 1 for a hierarchical list of nearest relatives). Patients with long-term incapacity are not included in this trial so patients that have appointed a Welfare Attorney or Guardian will not be eligible.

Section 6.1.2 of this protocol explains the process for including patients without capacity in England, Wales and Northern Ireland and Scotland.

Some pillars within the ROSSINI-Platform will include children and young people aged between 12 and 16 years. In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004, individuals under the age of 16 are not legally permitted to provide consent to participate in a

CTIMP. Therefore, informed consent will be obtained from a parent, guardian, or an individual with parental responsibility, or, where appropriate, a legally authorised representative. In addition to obtaining legal consent, assent will be sought from all children and young people aged 12 to 16, in line with best ethical practice. Assent refers to the child's affirmative agreement to participate and is not a legal substitute for consent. Potential participants between age 12 and 16 will be provided with age-appropriate information about the trial, including its purpose, procedures, potential risks and benefits, and their right to withdraw at any time. Where a child is judged to be capable of understanding the information provided (i.e. Gillick competent), their views will be given significant weight in the decision-making process. However, for CTIMPs, legal consent must still be obtained from a parent or legal representative regardless of the child's competence.

It is the responsibility of the local PI or the local Pillar lead to obtain informed consent/assent for each participant prior to performing any trial related procedures. This task can be delegated by the PI or the local Pillar lead to other members of the local research team (e.g. consultants, surgical registrars, research nurses and other allied health professionals), if local practice allows and this responsibility has been both delegated and documented on the ROSSINI-Platform Pillar Specific Site Signature and Delegation Log. All those delegated to take informed consent/assent must have undertaken Good Clinical Practice (GCP) training.

6.1 Consent procedure

6.1.1. Patients able to provide informed consent (Adults)

All potentially eligible patients will be approached for recruitment to ROSSINI-Platform. A Patient Information Sheet (PIS; either in paper or electronic format) will be provided to facilitate this process. To support understanding, a brief animated video summarising the key elements of the PIS may also be made available.

Investigators will ensure that they adequately explain:

- That consent is sought for inclusion in a randomised controlled trial
- That the trial will compare different interventions aiming to reduce SSI rates
- That the interventions will be allocated at random and the patient may be blinded to the allocation. Blinding is dependent on the interventions being used, the explanation of blinding will be tailored to the Pillar and interventions under study.
- What the trial will involve for the patient.
- That the patient (or nominated individual) will be required to engage with the CDWH for collection of follow-up data.
- The anticipated benefits and potential risks of taking part in the trial.
- That the patient will not be offered reimbursement of any expenses occurred as a result of participating in ROSSINI-Platform.
- That participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time.

The participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team if they wish. The participant has the opportunity to ask questions before the latest version of the of the ROSSINI-Platform Informed Consent Form (ICF) is completed. Due to the nature of the study (e.g inclusion of emergency patients, patients undergoing unplanned caesarean section) the time between patient approach and consent/assent may be limited. Therefore, no minimum time between the patient and/or parent/guardian (or legal representative) being given the information sheet for the trial and consent/assent being obtained. In these circumstances it is the responsibility of the person taking consent/assent to judge whether the potential participation has understood and willingly provided consent/assent.

Electronic and paper copies of the PIS and ICF will be available from the ROSSINI-Platform Trial Office. The PIS and ICF need to be printed or photocopied onto the headed paper of the local institution, and this can be done by either the site or staff at the ROSSINI-Platform Trial office..

6.1.2. Patients able to provide informed consent (Children and young people aged between 12-16)

Prior to any study-specific procedures, the parent(s) or legal guardian(s) of each potentially eligible child will be approached by a member of the ROSSINI-Platform research team. A comprehensive Parent/Guardian Information Sheet will be provided in paper or electronic format, outlining the study's purpose, procedures, potential risks and benefits, data protection measures, and the voluntary nature of participation. A brief animated video summarising the key elements of the information sheet may also be made available to support understanding. Adequate time will be given for the parent(s)/guardian(s) to review the information, ask questions, and consider participation. Written informed consent will be obtained from the parent(s)/guardian(s) prior to any study-related activities.

Investigators will ensure that they adequately explain to the parent(s)/guardian(s):

- That they are being asked to provide consent on behalf of the child/young person.
- That they understand the objectives, risks of the trial and the conditions under which it will be conducted.
- That they have been informed of the right to withdraw the child/young person from the trial at any time.
- That they have a contact point where further information about the trial can be obtained.

Where appropriate, age-appropriate PISs and Assent Forms will be provided to the child/young person. The research team will explain the study in a manner suitable to the child/young person's age, maturity, and psychological state. Assent will be sought from those who are capable of providing it, in accordance with local ethical and regulatory requirements. The child/young person's willingness to participate will be respected at all times, even if parental consent has been obtained.

All consent and assent discussions will be documented in the participant's medical records and/or study file, including the version of the information sheet used, the date of consent/assent, and the names of those involved in the process.

6.1.3. Patients unable to provide informed consent (Northern Ireland, England, Scotland and Wales)

Some patients who are eligible for the trial will have a temporary impairment to their ability to provide consent. This impairment will result from the condition for which they require surgical intervention. Patients who have a long-term cognitive impairment that prevents fully informed consent will be excluded from the trial.

If the patient does not have capacity for fully informed consent due to temporary impairment, where possible the trial will be briefly discussed with them, and they will be given the Summary PIS. In accordance with guidelines from the Health Research Authority (HRA), the trial will also be discussed with the patient's legal representative. The legal representative will be asked if the patient has expressed any prior wishes with regard to participating in research and if the patient has expressed a preference, this will be adhered to.

The legal representative must be:

- Told that they are being asked to give consent on behalf of the incapacitated adult.
- Told that they are free to decide whether they wish to make this decision or not, and
- Told that they are being asked to consider what the adult would want, and to set aside their own personal views when making this decision.
- Given sufficient information, in an understandable form, about the trial to ensure that they provide informed decision.

A legal representative Information Sheet will be provided to facilitate the assent process. If the legal representative agrees that the patient can be included in the trial, the legal representative will initial, sign and date the latest version of the legal representative consent Form.

If no legal representative is available, the patient will not be included in the trial.

It is imperative that when a legal representative has been consulted, that as soon as the participant is able to provide informed consent, the trial is explained to them and their written informed consent is sought. The participant will be given the PIS for delayed consent and their consent will be documented through the initialling, signing and dating of the latest version of the ICF for delayed consent.

If, at any stage, the participant refuses consent for involvement in the trial or asks to be withdrawn from the trial, their wishes must be adhered to.

For a small number of participants, it is anticipated that they will not regain consciousness/capacity within 30 days, as these patients will have already received the intervention and reached the primary endpoint, their data will be retained for use in the final analysis. If these patients regain capacity within the 90-day follow-up, where practical, the local research team will consent them for their involvement in the study.

6.1.4. Participants attaining 16 years of age during follow-up

In accordance with ethical and regulatory requirements, participants who reach the age of 16 during the course of trial follow-up will be asked to re-consent to continued participation. This will be conducted using the ROSSINI-platform ICF alongside the corresponding PIS. The re-consent process must be documented in the participant's medical records. A copy of the signed ICF will be provided to the patient, filed in the patients' medical notes and retained in the ISF. Additionally, subject to participant consent, a copy of the ICF will be forwarded to the trials office at BCTU or uploaded onto the electronic database

6.1.5. When a patient regains capacity

In all cases an assessment will be made at site, by the PI or a member of the site research team delegated the responsibility of consent on the Site Signature and Delegation Log, to determine whether the patient has regained capacity and is able to consent for themselves. Where this is found to be the case the research team at site will seek consent from them, at the earliest opportunity. The participant will be provided with the current ethically approved PIS and ICF. The processes outlined in section 6.1.1 should be followed. The legal representative should be informed of this at the outset. Should the patient express a view that they no longer wish to take part in the ROSSINI-Platform trial; their opinion will supersede that of the legal representative.

6.1.6. Patients who do not survive

The most challenging ethical consideration in this trial relates to the inevitable death of some patients. Consent will always be obtained prior to the participant being randomised, however in some instances this may have been provided by a legal representative who is not related to the participant . Actively seeking out and informing relatives of trial participation is transparent and avoids potential distress were the family to discover at some future point that their family member/relative had been involved in a clinical trial. However, informing the family/relatives/friends of trial participation in the immediate aftermath of their family member's/relative's/friend's death will impose an additional emotional burden at a time of great distress. Previous and ongoing emergency care trials have used passive information approaches, placing information in publicly accessible locations and in sites likely to be visited by relatives of the deceased (hospitals, GP surgeries, the offices of the Registrars of Births and Deaths). Such information contains brief details of the trial and contact details for those wishing to seek further information. This allows a family member/relative/friend to make an individual decision as to whether to seek further information regarding their family member/relative/friend, at a time of their choosing. This is the approach that we will take with the ROSSINI-Platform trial and a Research Ethics Committee (REC) approved poster will be placed in appropriate locations of participating sites.

6.2 Consent/assent documentation

Consent/assent will be obtained before any patient joins the trial. If the potential participant expresses an interest in participating in the trial, and has been confirmed as eligible to participate, consent can be taken in a number of different ways.

6.3 Face to face consent

- **Face-to-face consent/assent - Method 1 (on paper) (Participant/legal representative/parent/guardian)**

The latest version of the ICF is given to the participant/legal representative / parent/guardian and they will initial, sign and date the ICF. The PI or delegate consenting the participant will then sign and date the ICF.

- **Face to face consent/assent – Method 2 (electronic) (participant/legal representative/parent/guardian) - Preferred method**

Consent can be taken and recorded electronically via an online method known as eConsent within the ROSSINI-Platform system. The eConsent form will consist of checkboxes to indicate consent for each aspect of the trial. The patient/legal representative/ parent/guardian will be asked to electronically sign and date the latest version of the ICF which will be made available to all participating sites online. The PI or delegate will then also electronically sign and date the ICF via the trial system.

A copy of the signed ICF will be emailed to the participant/legal representative/parent/guardian or a hard copy provided, as per the participant's preference.

- **Face to face consent/assent – Method 3 (verbally) (participant/legal representative/parent/guardian)**

This consenting process may also be used in emergency situations when it is not possible to sign and date a consent form. In the emergency situation where time is limited, verbal consent for the intervention will be obtained prior to randomisation with written consent to continue with the trial taken following the surgical procedure and before discharge.

In an emergency, where verbal consent is being taken, a suitably qualified doctor, who has signed the ROSSINI-Platform Site Signature and Delegation Log, will discuss the study with the participant. A verbal discussion will include confirmation that the participant understands the information regarding the trial, understands that the choice of intervention will be made randomly and is happy to take part. This conversation must be recorded in the patient notes.

After the procedure, a PIS will be provided highlighting the follow-up and confirmation of willingness to continue to participate. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. If the participant is happy to continue to participate in the trial, the participant will be asked to sign and date the latest version of the ICF. Details of the informed consent discussions will be recorded in

the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIs given to the participant and version number of the ICF signed and date consent received.

6.4 Remote consent

- **Remote consent/assent – Method 1 (electronically) (participant//legal representative/parent/guardian)**

Where the consultation is undertaken remotely, the potential participant/legal representative parent/guardian will be asked to provide their e-mail address and the person taking consent will enter the e-mail onto the trial Electronic Data Capture (EDC) for a unique electronic link to be sent to the participant/legal representative/parent/guardian for them to access the ICF and ask them to complete it electronically. Once the potential participant has completed the ICF, the person taking consent will electronically countersign the ICF.

- **By post/ email/ telephone – Method 2 (participant/legal representative/parent/guardian)**

The ICF is posted or emailed (and then printed) to the participant/legal representative/parent/guardian along with the PIS. During a telephone discussion between the person consenting and the participant/legal representative/parent/guardian, the participant/legal representative/parent/guardian will initial, sign and date the ICF. The PI or delegate will document this in the participant's medical notes. The participant/legal representative/parent/guardian will then post or email the partially completed ICF back to the site. The PI or delegate who consented the participant will then print (if ICF emailed to site), sign and date the ICF. Only after the PI or delegate has countersigned the returned ICF is consent considered to be obtained.

- **Remote consent/assent – Method 3 (verbally) (participant/legal representative/parent/guardian)**

In cases where the potential participant/legal representative/ parent/guardian does not have an e-mail address or access to the internet, they will be asked to provide consent verbally, after the person taking consent has read out each of the statements on the ICF to the potential participant in the presence of a witness. The witness will verify that informed consent has been taken; the witness does not need to be named on the Signature Site and Delegation Log. As the potential participant agrees with each statement, the person taking consent initials the associated box of the electronic consent form. The ICF will then be electronically signed by both the person taking consent and the witness.

6.5 Both face to face and remote consent/assent (participant/legal representative/parent/guardian)

Only after the PI or delegate has countersigned the ICF is consent/assent considered to be obtained.

For both face to face and remote consent/assent, agreement to each section of the ICF will be entered onto the trial database. The potential participant must give explicit consent for the regulatory authorities, members of the research team and/or representatives of the sponsor to be given direct access to the participant's medical records.

In addition, the participant understands and acknowledges that a copy of the signed ICF may be transferred to the ROSSINI-Platform Trial Office for review.

Consent for the participant's preferred method of contact, i.e., e-mail address and/ or mobile number will be obtained in order to send participants online links to complete the electronic questionnaires .

Once the participant is entered into the trial, the participant's signed ICF will be stored in the site-specific section of the trial database. The participant's trial number will be linked to the consent form stored in the trial database. The participant's trial number will be entered on the copy of the ICF that is maintained in the Investigator Site File (ISF), and a copy will be filed in the participant's medical notes. Sites can download and print the completed ICF from the trial database.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to the participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

6.6 Ongoing consent (participant/legal representative/ parent/guardian)

At each visit, the participant's willingness to continue in the trial will be ascertained (through the legal representative parent/guardian as appropriate) and documented in the medical notes. Throughout the trial, the participant, or legal representative/parent/guardian will have the opportunity to ask questions about the trial.

Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participant's decision to continue, the participant, or legal representative/parent/guardian will be given time to consider and if happy to continue they will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

In the UK, if a participant loses capacity during the 30 day study period, consent of a Legal Representative on whether the participant should remain in the study will be sought and a consent obtained as described in sections 6.1.2 and 6.1.3.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local institution.

With the participant's consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

6.7 Additional consent (participant/legal representative/ parent/guardian)

Additional statements are included in the ICF for the participant/legal representative/parent/guardian to acknowledge that they understand that the Trial Office might in the future, for other related research, collect participant data available in NHS routine clinical datasets, including primary care data (e.g., Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS Digital and other central UK NHS bodies. The participant /legal representative/parent/guardian will acknowledge that they understand that the Trial Office might send their name, address, date of birth and NHS number to the relevant national registry, and then for the national registry to link this to their data and send the information back to the Trial Office. The acknowledgement by the participant/legal representative/ parent/guardian will also allow access to other new central UK NHS databases that will appear in the future. This will allow us (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without needing further contact with the trial participants.

7. ENROLMENT, RANDOMISATION and BLINDING

7.1 Identification

Potentially eligible participants will be identified at the time they are listed for surgery by a member of their direct clinical care team. This may be a surgeon, surgical trainee, consultant, nurse, other allied health professionals or, in the obstetric pillar, participants can also be identified by a midwife. It is envisaged that the majority of patients will be screened and recruited in four scenarios:

1. Surgery outpatient clinics, – by a consultant or trainee surgeon when the patient is being booked for elective surgery.
2. Pre-assessment clinic – by a nurse, allied health professional (AHP) or surgical trainee when the patient is being assessed for surgery.
3. Planned theatre lists – by a consultant or trainee surgeon or AHP once a patient has been listed for surgery and arrives in hospital, i.e. at the time of admission for surgery.
4. In the emergency setting (assessment unit or emergency department) – by a consultant or trainee surgeon or associated AHP when a decision to operate is made.

7.2 Screening

Potentially eligible patients will be identified by a member of their direct clinical care team. The clinical team will inform the patient about the study and request permission for a member of the research team to discuss the study with them. Patients will be approached for entry into the trial by an appropriate GCP-trained member of the research team delegated this responsibility on the Pillar-Specific ROSSINI-Platform Site Signature and Delegation Log. Eligibility for the trial must be confirmed by a suitably qualified medical practitioner (e.g. a consultant surgeon, surgical trainee) who is delegated the task on the Pillar-Specific ROSSINI-Platform Site Signature and Delegation Log.

The trial will be discussed with eligible elective patients preoperatively, either in the outpatient clinic at the time of listing for surgery, in the preoperative assessment clinic that patients attend routinely around 7-10 days prior to surgery, or at the time of admission for surgery.

In the emergency setting, the trial can be discussed with patients at the same time as operative consent, once a definitive decision for surgery is made.

In both settings, information will be provided in the form of a PIS and in some pillars, short, animated video. Patients will be given as much time as required to decide whether they wish to take part.

If the potential participant meets all the eligibility criteria and they or their legal representative confirms that they are willing to take part in the ROSSINI-Platform trial, they will be asked to formally consent/assent to participate in the trial as detailed in the CONSENT section (see Section 6).

Details of all patients approached about the trial will be recorded on the Pillar-specific ROSSINI-Platform Participant Screening Log which will be kept in the ISF and should be available to be sent to the Trials Office upon request. The Pillar-Specific ROSSINI-Platform Patient Screening Log should be maintained at each site using planned and electronic theatre lists.

7.3 Randomisation

Randomisation will be provided by BCTU using a secure online system (available at <insert web address>), thereby ensuring allocation concealment.

Unique log-in usernames will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the **ROSSINI-Platform Pillar Specific Site Signature and Delegation Log**. Unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details.

The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

Please note: to randomise a patient when the online system is down, the ROSSINI-Platform Trial Office should be contacted directly via email or telephone using the contact details outlined at the front of the protocol.

7.4 Randomisation Process

Once eligibility is confirmed and assent/consent has been received, the patient can be randomised into the trial. Randomisation should occur as close to the time of surgery as possible, ideally around the time of induction of anaesthesia on the day of surgery. This helps minimise crossover or lack of compliance with treatment allocation.

A ROSSINI-Platform Pillar Specific Randomisation worksheet which replicates the electronic randomisation form, may be used to collate the necessary information prior to randomisation. All

questions and data items on the online Randomisation Form must be answered appropriately prior to a potential participant being randomised into the trial and a Trial Number being issued.

Following randomisation, a confirmatory e-mail will be sent to the local PI, the Site Pillar Lead, responsible clinician (i.e. the consultant responsible for the patient's care), the research nurse or midwife and the person who performed the randomisation. The confirmatory email will also be sent to the ROSSINI-Platform trial mailbox.

The local research team should add the participant to the ROSSINI-Platform Pillar Specific Participant Recruitment and Identification Log which links participants with their Trial Number. The Site Pillar Lead PIs must maintain this document securely and it must not be submitted to the Trial Office. The ROSSINI-Platform Pillar Specific Participant Recruitment and Identification Log should be held in strict confidence.

7.4.1 Randomisation method

It is possible that, in some surgical procedures, more than one wound may be created. However, the implementation of potential strategies to randomise individual wounds within a participant could increase the risk of compromising data validity. Acknowledging that, from a participant perspective, the presence or absence of any wound infection is the primary concern, it was therefore decided to randomise participants at the individual level and to collect an overall outcome based on the presence of any wound infection in the participant.

There are three interventions being tested within each pillar. Specific details of the individual pillar interventions are described in each PSP. To account for the possibility that interventions may be discontinued following interim analyses or that additional interventions may be introduced in the future, as well as the fact that participants may not be eligible to receive all three interventions, we implemented a concurrently randomised cohort (CRC) structure within the randomisation procedure to indicate into which combination of randomisations a participant is entering. Initially, this comprises seven separate CRCs to accommodate the three interventions and their various combinations. Participants will be randomised in a 1:1 ratio separately for each of the three interventions (e.g. "intervention A" vs not "intervention A"), and may therefore be allocated to receive any combination of 0, 1, 2 or all 3 of the interventions available in a pillar depending on the CRC to which they belong. See Table 1 for further details.

Within each pillar RCT a minimisation algorithm will be used within the randomisation system to ensure balance in the intervention allocations. The variables are pillar specific and are defined within each PSP.

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.

Table 1 - Separate randomisation schedules

	Interventions	**Randomised Groups**

CRC 1	A, B, C	A, B, C, A&B, A&C, B&C, A&B&C, None
CRC 2	A, B	A, B, A&B, None
CRC 3	A, C	A, C, A&C, None
CRC 4	B, C	B, C, B&C, None
CRC 5	A	A, None
CRC 6	B	B, None
CRC 7	C	C, None

7.5 Blinding

In the ROSSINI-Platform trial outcome assessment post-discharge is undertaken remotely by the CDWH by blinded outcome assessors.

It is not possible to blind the operating surgeon to the intervention(s) allocation.

It is also not possible to ensure blinding for outcome assessors at discharge, given the nature of the interventions under study as the randomised allocation may be evident.

Blinding of the participant will be maintained as far as is feasible but is dependent upon the interventions used within each pillar.

Any specific measures taken per intervention to maintain blinding are described within each PSP.

7.5.1 Blinded personnel

The post-discharge up to Day 30 wound review will be undertaken by a trained wound assessor through the CDWH who will be blind to treatment allocation and who has not previously been involved in the care of the participant.

The importance of blinding will be explained to participants, and they will be asked to not inform the wound assessor of their treatment arm.

7.5.2 Unblinding

Participants can be unblinded upon request at the end of the trial, (or earlier if for legal reasons), which is once the final participant has completed all follow-up, and the database is locked for final analysis.

7.6 Informing the participant's GP and other parties

If the participant has agreed, the participant's GP should be notified that they are in the ROSSINI-Platform trial, using the ROSSINI-Platform Trial GP Letter. The GP letter will not state which interventions the participant was allocated to.

The ROSSINI-Platform Trial GP Letter will be sent to the participant's GP directly from the site that randomised the patient into the trial.

No other parties outside of the trial team will be informed of the participant's entry into the study.

8. TRIAL INTERVENTIONS

The trial interventions within the ROSSINI-Platform trial are pillar-specific, therefore they are detailed within the PSP.

9. OUTCOME MEASURES

9.1 Internal pilot outcomes

The feasibility of the internal pilot will be assessed at three levels: the platform, per pillar and per intervention.

At PLATFORM level

At Platform level, we are aiming to:

- Open at least 12 sites
- Recruit at least 250 patients
- Have over 95% engagement with the CDWH.

At 3-months post commencement of recruitment of the first patient to the platform, the Executive Trial Management Group (ETMG) and Trial Steering Committee (TSC) will review the pilot data against the platform-level pre-specified Red-Amber-Green (RAG) progression criteria (Table 2).

Table 2 - PLATFORM-LEVEL Internal Pilot Progression Criteria

Progression Criteria	Number of sites opened platform-wide	Overall recruitment to the platform	Engagement with CDWH *
GREEN (GO)	≥ 12 sites	≥ 250 participants	≥95%
AMBER (modify)	7-11 sites	121 – 249 participants	≥90 % - <95%
RED (REVIEW)	≤ 6 sites	≤ 120 participants	< 90%

*Percentage of participants submitting at least one response to the CDWH

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.

9.2 Main trial outcomes

9.2.1 Primary outcome(s)

The primary outcome is SSI within 30 days of surgery, as defined according to a modified 2017 Centers for Disease Control (CDC) and Prevention criteria. Whilst several systems exist to define SSI, the internationally recognised CDC definitions are the current gold standard for SSI assessment and have been used in a number of multicentre randomised trials.

The following CDC definition will be used in ROSSINI-Platform to identify deep incisional or superficial incisional SSIs:

1. The infection must occur within 30-days of the index operation
   AND
2. The infection must involve the skin, subcutaneous, muscular or fascial layers of the incision
   AND
3. The patient must have at least one of the following:
   • Purulent drainage from the incision
   OR
   • Wound opened spontaneously or deliberately by a clinician
   AND the patient has at least one of: pain or tenderness; localised swelling; erythema or heat; fever (>38°C).
   OR
   • Organisms are cultured from a culture taken from the wound using an aseptic technique
   OR
   • Diagnosis of SSI by a clinician or on imaging

Surgical site infection in ROSSINI-Platform encompasses both superficial and deep incisional wound infections. In practice, a deep incisional infection will manifest alongside a superficial one and can be viewed as a more severe subset of the latter. We will not seek to differentiate between deep and superficial SSI as our interventions seek to prevent both.

The trial does not include organ space infections* as an outcome measure; this is a rare complication when compared with superficial/deep infections and importantly, organ space infections are not likely to be affected (positively or negatively) by the interventions chosen for ROSSINI-Platform.

*According to CDC definition, organ space definition in obstetrics includes endometritis, see the OBSTETRIC PSP for the outcome definition of endometritis.

9.2.2 Secondary outcomes

- 30-day and 90-day postoperative mortality rate (POMR).

- 30-day postoperative worst wound complication (Clavien-Dindo classification for vascular groin, LLA, breast, cardiac and obstetrics; Landriel-Ibanez[33] classification for neurosurgery).
- Risk of wound or intervention only related Serious Adverse Events up to 30 and 90 days post-surgery.
- Length of hospital stay after surgery as measured from the date of surgery to the date fit for discharge from primary site collected via hospital records.
- Risk of hospital re-admission for wound related complications within 30 and 90 days post-surgery..
- Risk of wound reopening and/or re-operations within 30 and 90 days post-surgery.
- Preference-based Quality of Life (QoL EQ-5D-5L) collected at Baseline, Day of Discharge andweekly until Day 30 post-surgery via the CDWH.
- Cost effectiveness (Resource Use Questionnaire; RUQ).

9.2.3 Definitions and Timings

30-day postoperative mortality rate

The 30-day POMR is determined as death of a patient within the first 30 postoperative days, with day of surgery taken as day 0. POMR has been highlighted as a key performance indicator by the Lancet Commission on Global Surgery and recommended for use in all international clinical trials in surgery. In the ROSSINI 1 trial, with similar participant inclusion criteria, the POMR was 2.6%[34].

30-day postoperative worst wound complication

The 30-day postoperative worst wound complication is determined as the highest level Clavien-Dindo grade complication (classified as I to V) measured in the first 30 postoperative days, with day of surgery taken as day 0. The Clavien-Dindo classification will be used in all pillars except Neurosurgery where classification will be according to the Landriel-Ibanez classification where complications are classified as I to IV. Any deviation from the normal postoperative course that has an adverse effect on the patient's wound and is not either a treatment failure or sequel, is a complication. The Clavien-Dindo classification determines the severity of a complication based on the therapeutic consequence of that complication[35] . This has been validated internationally across health settings with high reproducibility and low interrater variability. The Landriel-Ibanez classification is based on Clavien-Dindo, but modified to conform with neurological procedures and neurosurgery appropriate outcomes.

Health-related, preference-based quality of life

QoL will be assessed using the widely validated EuroQol EQ-5D-5L questionnaire at baseline (preoperative), as an inpatient at discharge and then weekly until Day 30 post-surgery. If the patient has an ongoing SSI 30-days post-surgery, then the EQ-5D-5L questionnaire will be completed every 30 days until the wound has fully healed (e.g. Day 60, Day 90, Day 120 etc.). This ongoing follow-up will continue to a maximum of 120 days post-surgery.

Cost-effectiveness

The cost effectiveness of the interventions will be assessed in an economic evaluation (see section 16 for further details). This cost per Quality Adjusted Life Year (QALY) analysis has been used in both the ROSSINI 1 and 2 trials[26] . The economic evaluation will be populated with Resource Use Questionnaire (RUQ) which collects patient-level health resource usage both in primary and secondary care, and QALYs will be derived from EQ-5D-5L responses.

10. TRIAL PROCEDURES

Patient on-boarding:

Prior to discharge, research nurses (or any member of the site research team delegated the task on the Pillar-Specific ROSSINI-Platform Site Signature and Delegation Log) will activate the submission schedule on Isla, the digital platform used for remote wound assessment by the CDWH. While still in hospital as close to the day of discharge as possible, participants will conduct a 'practice run' for submitting information and receiving replies from the CDWH team (the hub). A skin tone tag will be added to Isla by the research nurse, or other delegated site research team member, using the modified Ho & Robinson Tool, as measured against the participant's inner arm.

Participants can choose to nominate family and friends who may be more skilled with smartphones, able to take photos of wounds in awkward places or help with language. The email and/or telephone number of the family member or friend will be entered into Isla. Isla is connected to the NHS Spine. A member of the site research team enters the participant's contact details onto Isla, and the pre-programmed weekly schedule is activated. There is no need to install or download anything. Participants will have access to the National Wound Care Strategy Programme & Participant Experience Network leaflet, available in thirteen languages, which offers guidance on capturing good wound pictures. The system incorporates a 'privacy blur' feature which can be used when capturing sensitive areas, such as the breast or groin.

Day of Discharge

- In-hospital SSI review

On the day of discharge, participant's notes should be reviewed to determine if they experienced an in-hospital SSI. For those participants who experience an in-hospital SSI, confirmation of this will be recorded on Isla, participants will receive reminders to complete QoL questionnaires on a weekly basis, however they will not be expected to submit further information about their wound.

- Day of discharge wound review

If local practice allows, a wound assessment should be performed on day of discharge. The wound will be assessed by a blinded member of the research team for an infection according to the modified CDC SSI criteria via completion of the wound assessment questionnaire on Isla.

Although it may not be feasible to blind either the participants or the inpatient wound assessors to the treatment allocation(s) on the day of discharge because an intervention may still be present and

clearly identifiable, the importance of blinding will be explained to participants, and they will be asked to not inform the wound assessor of their treatment arm. The assessment will be undertaken by a member of the research team or clinical investigator who must have signed the ROSSINI-Platform Pillar specific Site Signature and Delegation Log.

- Quality of Life

The EQ-5D-5L should be completed on the day of discharge, if feasible for the pillar at the participating site.

After discharge:

Once at home, participants will receive weekly invitations to submit triage information about their wounds in response to pre-programmed SMS text message requests or via email, depending on their preference. Weekly requests will continue until Day 30 post-surgery. Requests will be sent at Day 7, Day 14, Day 21 and Day 30. Participants can also provide information between scheduled requests if they observe any changes in their wounds.

At the same scheduled weekly interaction, participants will also be asked to complete the EQ-5D-5L questionnaire.

The submitted wound information and photo, if submitted, undergoes review by a member of the CDWH team (the hub). Participants are not required to remove their dressings for the wound photos.

The hub team will be blinded to which intervention the participant received. Participants may be contacted for additional information, recommended to seek further treatment, or assured that their wound is healing normally. For those who cannot use digital monitoring, contact will be made via telephone alone to ensure no digital exclusion. A member of the hub team will edit out any identifiable features (such as faces or tattoos) submitted by participants before saving the data in Isla to ensure compliance with ethical guidelines and privacy regulations.

Patients who are still an inpatient at Day 30 post-surgery

Those participants who are still an inpatient at Day 30 post-surgery, will not be onboarded to Isla or followed up through the CDWH.

Instead, an in-patient wound assessment will be performed on Day 30 by a member of the site research team and reported on the ROSSINI-Platform Day of Discharge (or 30 Day) electronic Case Report Form (eCRF).

Day 90 review

At Day 90, a clinical notes review will be undertaken to collect data including re-admissions to hospital, re-interventions, SSIs and complications.

10.1 Schedule of assessments

Table 3 - Schedule of assessments

Contact	Preoperative (Elective and emergency surgery)	At surgery	Day of discharge*	Post-discharge follow-up (Every 7 days until day 30 post-surgery +/-3 days) via CDWH	Ongoing SSI (Every 30 days + 7 days until resolution via CDWH)[+]	90 Day Review (Day 90) +/- 14 days
Eligibility confirmation	**X**					
Patient Information Sheet provided	**X**					
Informed Consent[++]	**X**	X[£]	X	X	X	
Baseline (BASELINE eCRF)	**X**					
Randomisation (RANDOMISATION eCRF)		**X**				
Operation (IN-THEATRE eCRF)		**X**				
Patient onboarding to Isla			**X**			
In-hospital Wound Assessment (Wound Assessment via Isla)**			**X****			
Blinded Wound Assessment (via Isla)				X[&]	**X**	

Contact	Preoperative (Elective and emergency surgery)	At surgery	Day of discharge*	Post-discharge follow-up (Every 7 days until day 30 post-surgery +/-3 days) via CDWH	Ongoing SSI (Every 30 days + 7 days until resolution via CDWH)[+]	90 Day Review (Day 90) +/- 14 days
Serious Adverse Event Reporting (SAE eCRF)		**X**				**X**
Day 90 Follow-up via medical notes review (DAY 90 eCRF)						**X**
Questionnaires:						
Quality of Life Questionnaire (EQ-5D-5L)	**X^**		**X^^**	**X**	**X**	
Resource Use Questionnaire (RUQ)[$]				**X**	**X**	

[£]Informed consent refers to all methods of consent and assent used within the Platform, e.g. verbal, written. Consent may also be delayed in some cases. In such circumstances consent will be requested as soon as the participant is able.

[+]Until a maximum of 120 days post-surgery. A subset of participants without an SSI will also be followed up to this timepoint.

[++]It is important to also reaffirm consent at each trial visit.

* At Day of Discharge or Day 30 post-surgery if the participant is still an in-patient

** Wound assessment at discharge if aligns with local practice.

*** Wound assessment data collected here should be applicable and relevant between Day 0 (day of surgery) to Day of Discharge.

[$] Wound assessment is via Isla and will not involve the site research team.

[$$] Requests will be sent at Day 7, Day 14, Day 21 and Day 30. With reminders at 24hrs and 48hrs after request and the questionnaire 'open' for 7 days to allow participants to provide information between scheduled requests if they observe any changes in their wounds.

^ Quality of Life (QoL) at Baseline should be completed after consent but before surgery.

^^ All participants, including those who have had an in-hospital SSI, should complete QoL.

[&] Resource usage questionnaires will not be requested within the pilot stage.

10.2 Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a *particular* aspect of the trial.

Participants found to be ineligible post randomisation should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation.

The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention (where applicable), but is willing to be followed up in accordance with the schedule of assessments (Table 3) and if applicable using any central UK NHS bodies for long-term outcomes (i.e.

the participant has agreed that data can be collected and used in the trial analysis).

No trial related follow-up: The participant does not wish to attend trial visits in accordance with the schedule of assessments, but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e. only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes of levels in participation within trial (date, reason and category of status change) should be clearly documented in the source documents.

If a family member/ friend who has provided their contact details to allow onboarding and data collection via the CDWH withdraws their consent, then their details will be removed. Participants can provide alternative contact details or withdraw from trial related follow-up.

If a participant loses capacity during the study, data previously collected will be retained. Ongoing collection of patient reported outcome measures (PROMs) will not be carried out, but information from hospital documentation of unplanned readmission, complications, and mortality, will be collected and used in the analysis.

11. ADVERSE EVENT REPORTING

11.1 Definitions

Table 4 - Definitions for Adverse Events

Severity Definitions	Mild Moderate Severe	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae. A sign or symptom, which interferes with the participant's usual activity. Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant administered a trial intervention and which does not necessarily have a causal relationship with this intervention. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of trial intervention (which may be an investigational medicinal product (IMP)), whether or not related to the trial intervention (which may be an IMP).
Adverse Reaction	AR	All untoward and unintended responses to a trial intervention or an IMP related to any dose administered. Comment: An AE judged by either the reporting Investigator or Sponsor as having causal relationship to trial intervention qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: Results in death

		Is life threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Is a congenital anomaly/birth defect Or is otherwise considered medically significant by the Investigator**
Serious Adverse Reaction	SAR	An AR which also meets the definition of a SAE.
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e., the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above

11.2 Adverse event recording – general

The recording and reporting of AEs will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of GCP as set out in the UK Statutory Instrument (2004/1031 and subsequent amendments) and the requirements of the HRA and The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments thereof.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

11.3 Adverse event reporting period for the ROSSINI-Platform

The reporting period for AEs and SAEs in ROSSINI-Platform will be:

- From day of surgery (when the interventions were administered) until the end of trial follow-up (90 days later).

The overall defined reporting period will end 90 days post-surgery. After the participant has reached 90 days post-surgery, sites will not be actively following up participants for SAEs.

11.4 Adverse Events (AE) reporting in the ROSSINI-Platform

AEs are commonly encountered in participants undergoing vascular groin, LLA, obstetric, breast, cardiac and neurosurgery. As the safety profiles for this trial population and the interventions used in this trial are well characterised, and will not affect the safety of participants, a strategy of targeted reporting of AEs will be used.

Expected AEs that are infection and wound complication related will be recorded on the relevant CRFs as part of the outcome measures for this trial, these include:

Infection related:

- Pain or tenderness at the incision site
- Localised swelling
- Redness at the incision site
- Heat at the incision site
- Fever
- Surgical site occurrence excluding infection (hematoma, seroma, wound dehisence)
-

11.5 Serious Adverse Events (SAE) reporting in the ROSSINI-Platform

It is recognised that the frequency of SAEs in this participant population may be high. Many of these SAEs will be anticipated due to the potential complications of the surgery. We have therefore outlined anticipated SAEs that do not require reporting and anticipated SAEs that do not require expedited reporting.

For all SAEs, the PI or delegate must do one of the following:

1. **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the trials office as per Section 11.5.1 Serious Adverse Events not requiring reporting to the Trial Office.

2. **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 11.5.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office.

3. **Report SAEs to the trial office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per Section 11.5.3 SAE Reporting Process.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention(s) or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

11.5.1 Serious Adverse Events not requiring reporting to the Trial Office

Some events that meet the definition of an SAE will not require reporting to the Trials Unit.. If any of the events outlined below in Table 5occur during an individual's participation, from the date of surgery through to end of follow-up, reporting the event is NOT required as these events are not considered to be critical to evaluations of the safety of the trial:

Table 5 - SAEs that do not require reporting

Expected SAE	Process
Pre-planned hospitalisation	Document in medical notes only
SAEs related to pre-existing condition	

All events which meet the definition of serious must be recorded in the participant medical notes, including the causality and severity, throughout the participant's time in the trial, including follow-up, but for trial purposes these events do not require reporting. Such events are "safety reporting exempt".

11.5.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition or surgery), and the SAE, may be known. That is, such events are protocol-defined as "expected" (see Section 11.6.2 Assessment of expectedness of an SAE by the CI or Platform Pillar Lead).

Such events should still be recorded by the local research team in the participant's medical notes and on the relevant eCRFs, but do not require expedited reporting since the assessment of expectedness for the specified events has been pre-defined.

These include:

Table 6 - ROSSINI-Platform Trial SAEs requiring non-expedited reporting for all participants

Non-Expedited SAE	Process

Death (unrelated to the trial/ intervention(s))	Report on the In-Theatre eCRF, the Day of Discharge eCRF or the Day 90 eCRF (Trial specific eCRFs) and complete a SAE eCRF.
Interventions (either within theatre, radiology department or on the ward) to drain wound infections	
Thrombo-embolic events	
Infections not related to the wound (eg. pneumonia, urinary tract infections)	
Cardiac or central nervous complications	
Prolonged hospital stay as a result of wound infections	

11.5.3 Serious Adverse Events requiring expedited reporting to the Trial Office

Any SAEs **NOT** listed in Sections 11.5.1 and 11.5.2 must be reported to the ROSSINI-Platform Trial Office on a trial specific SAE eCRF within 24 hours of the site research team becoming aware of the event.

Table 7 - SAE that require expedited reporting

Expedited SAE	Process
Death (related to the trial / intervention(s))	Report on SAE eCRF and provide to the ROSSINI-Platform Trial Office within 24 hours of becoming aware of the event.
Skin Reactions	
Allergic reactions	
Combustion	

Any other event that meets the criteria of a SAE and is potentially related to any of the trial interventions must be reported to the trial office in an expedited manner.

11.6 SAE REPORTING PROCESS

On becoming aware that a participant has experienced an SAE which requires reporting on a SAE eCRF, the PI / Site Pillar Lead or delegate should report the SAE to their own Trust in accordance with local practice and to the ROSSINI-Platform Trial Office.

To report an SAE to the ROSSINI-Platform Trial Office, the PI / Pillar Lead or delegate must complete, date and sign the SAE eCRF via the ROSSINI-Platform Trial system trial system using the information below within the timeline specified in sections 11.5.2 and 11.5.3. Any other relevant, appropriately

anonymised, data should be submitted to the ROSSINI-Platform Trial Office using the ROSSINI-Platform Trial Mailbox (ROSSINI-Platform@trials.bham.ac.uk).

To report an SAE, the PI or delegate should:

Complete, date and sign the SAE form via the ROSSINI-Platform trial system

Please also Email ROSSINI-Platform@trials.bham.ac.uk to make the ROSSINI-Platform Trial Office aware that an SAE has been submitted, along with any other relevant anonymised documentation.

Where an SAE Form has been completed by someone other than the PI/ Site Pillar Lead (or medically qualified delegate) initially, the original SAE form must be countersigned by the PI/ Pillar Lead (or medically qualified delegate) to confirm agreement with the causality and severity assessments.

On submission of an SAE form, a unique reference number will be assigned. The site and the ROSSINI-Platform Trial office should ensure that the SAE reference number is quoted on all correspondence. The site should ideally e-mail the trial mailbox to inform the ROSSINI-Platform Trial office that they have submitted an SAE.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE reference number within 1 working day of reporting, the site should ideally contact the ROSSINI-Platform Trial Office.

Copies of the completed SAE form should be printed on resolution of the SAE and filed in the ISF.

11.6.1 Assessment of causality

When completing the SAE form, the PI / Site Pillar lead (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see Table 8: Categories of causality) of the event.

In defining the causality the PI / Site Pillar Lead (or medically qualified delegate) must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per Table 8: Categories of causality, all events considered to be ‘possibly’, ‘probably’, or ‘definitely’ related to the intervention will be reported by the trial office as ‘related’; all events considered at site to be ‘unlikely’ or ‘unrelated’ to the intervention will be reported by the trials office as ‘unrelated’. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 8 - Categories of causality

Category	Definition	Causality

Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form, the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) or delegate who will independently* review the causality of the SAE.

An SAE judged by the PI / Pillar Lead or CI or delegate to have a reasonable causal relationship ("Related" as perTable 8: Categories of causality) with the intervention will be regarded as a related SAE (i.e., SAR). The severity and causality assessment given by the PI / Pillar Lead will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's / Pillar Leads causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI / Pillar lead, an independent clinical causality review will be performed.

11.6.2 Assessment of expectedness of an SAE by the CI

The CI or delegate(s) will also assess all related SAEs for expectedness with reference to the criteria in Table 9: Categories of expectedness.

Table 9 - Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information. The Reference Safety Information (RSI) document will be Section 4.8 'Undesirable effects' (or the equivalent section) of the SmPC from the designated SmPC will be used as the RSI, if appropriate. The specific SmPC is detailed within the relevant PSP.
Unexpected	An adverse event that is not consistent with known information about the trial related procedures and is not listed in the RSI.

If the event is unexpected (i.e., it is not defined in the approved version of the RSI) and serious, it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The CI (or delegate) will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

11.6.3 Provision of SAE Follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Where significant new information is reported on the SAE eCRF, the PI (or medically qualified delegate) should also consider review and update of relatedness and causality as applicable. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted via the electronic trial management system, and a copy kept in the ISF.

11.7 Reporting SAEs to third parties

Data Monitoring Committee

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

MHRA, REC and RGT

The Trial Office will report details of all SARs (including SUSARs) to the Medicines & Healthcare Products Regulatory Agency (MHRA), Research Ethics Committee (REC), and UoB Research Governance Team (RGT) annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

Additionally, BCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, REC and RGT within 7 days of being notified. Follow-up information will be provided within an additional 8 days.

All other events categorised as non-life threatening/non-fatal SUSARs will be reported within 15 days of being notified.

The MHRA, REC and RGT will be notified immediately if a significant safety issue is identified during the trial.

Details of all SUSARs and any other safety issue which arises during the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

Intervention companies

The appropriate company will be notified of any SAEs that occur in participants treated with their product alone or in combination.

These will be forwarded on a regular basis (monthly or quarterly) and sent as a list of events. No patient identifiable information will be given to the company.

11.8 Urgent Safety Measures

The Clinical Trials Regulations make provision for the Sponsor and PIs to take appropriate Urgent Safety Measures to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the MHRA and REC.

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the reason why they have been taken.

11.9 Follow-up of pregnancies

Any participants that become pregnant from date surgery until 30 days after the last administration of an intervention will be followed up to outcome of the pregnancy. The outcome of these pregnancies will be recorded via the pregnancy notification form and in the event of congenital anomalies or birth defects these should be reported as an SAE.

Delegated site staff will complete the ROSSINI-Platform Pregnancy Notification and Outcome form as soon as the site becoming aware of the pregnancy. If consent has been given to monitor the pregnancy, the pregnancy outcome should be followed up to birth outcome. Consent to monitor the pregnancy, the mother's relevant medical history and any medication taken during the pregnancy will be documented in the participants' medical notes.

There is no requirement to report pregnancy in the partner of a male participant.

Standard routes for reporting of suspected side effects (including the yellow card scheme) will be available to investigators, as in routine clinical practice.

11.10 Emergency Unblinding

Emergency unblinding is not necessary within the ROSSINI-Platform as the interventions used (or not used) will be recorded on the electronic operation note for every patient in the trial.

12. DATA HANDLING AND RECORD KEEPING

12.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. These records can be in various forms, including paper documents, electronic records or other media. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Typically, the data provided on all eCRFs should routinely be recorded in the participant's medical notes, when this is not being conducted then data collected for the purpose of ROSSINI-Platform trial can be recorded on the ROSSINI-Platform paper worksheets. Data should then be transcribed to the Trial electronic data capture system (EDC) database and the data on the paper worksheet will be considered the source data and should subsequently be filed in the ISF.

Some data variables may be entered directly onto the eCRF, these are clearly identified and detailed below in Table 10: Source data in the ROSSINI-Platform Trial.

Source data is kept as part of the participants' medical notes generated and maintained at site. In addition, for this trial follow-up after discharge is done remotely via the CDWH. The data collected via the CDWH is via consultation with the participant, and is entered directly onto the Isla system by CDWH. As data is entered directly into the Isla system, Isla itself becomes the source document, this is because Isla is the first place where the data is recorded. Data collected via the CDWH includes review of the wound and triage information to determine if a SSI is present. Participants can submit photographs to facilitate wound review. Participants are also asked to complete QoL questionnaires weekly until Day 30 post-surgery. For those participants who have an ongoing SSI at Day 30, they will be asked to complete QoL questionnaires until resolution, but to a maximum of 120 days post-surgery. This data is stored on the Isla system.

Table 10 - Source data in ROSSINI-Platform

Data	Source
Participant Reported Outcomes (At baseline and discharge)	The original record of questionnaire completion is the source data. Questionnaires can be completed by participants electronically or on paper. If completed electronically the electronic record will be the source data, held on BCTU servers as part of the electronically-enabled questionnaire completion. If completed on paper, the paper record will be the source data and will be entered onto the trial database.
Participant Reported Outcomes (Post-discharge) via CWDH	The electronic record within the Isla system will be the source data.
Clinical event data (Pre discharge)	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Clinical event data (Post-discharge) via CWDH	The electronic record within the Isla system will be the source data.

Health economics data	Data will be completed directly on to the CRF by the participant and this will constitute the source data. The CRF is source data.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source documents (participant medical records).

12.2 Case Report Forms (CRF) completion

eCRFs should be completed within the ROSSINI-Platform trial system for each individual subject. Staff delegated to complete eCRFs will be trained to adhere to the eCRF completion guidelines. Worksheets will be provided to sites to aid with data collection only.

The eCRFs will include (but will NOT be limited to) the following forms (see Table 11 **Error! Reference source not found.**):

Table 11 - Case report forms in the ROSSINI-Platform Trial

Form Name	Schedule for submission
Screening Log	When a participant is being considered or approached to participate in the ROSSINI-Platform Trial.
Informed Consent	Prior to randomisation
Randomisation Form	At the point of randomisation
Baseline data form	As soon as possible after consent
In-Theatre Form	Completed during hospital stay for index surgery
Day of Discharge Form	As soon as possible after discharge.
Day of discharge participant reported outcome measures	As soon as possible on day of discharge.
Follow-up via the CDWH including participant reported outcome measures	Every 7 days post-discharge
Day 90 review Form	To be completed as close to Day 90 as possible (+/- 14 days) via clinical note review.
Resource Use Questionnaire:	As soon as possible after each assessment time point

Serious Adverse Event Form	If expedited: within 24 hours of site research team becoming aware of event If non-expedited: in accordance with section 11.
Pregnancy Notification Form	As soon as possible after becoming aware of participant's pregnancy
Pregnancy Outcome Form	As soon as possible after outcome of pregnancy and/or birth of the child
Trial Exit/Change of status CRF	At the point of becoming aware of withdrawal/change of status or death

An eCRF should be completed for each individual participant.

In all cases it remains the responsibility of the PI to ensure that the eCRF has been completed correctly and that these data are accurate. This will be evidenced by the signature of the Site PI, Site Pillar Lead "or delegate(s)". The Pillar specific Site Signature & Delegation Log will identify all those personnel with responsibilities for data collection.

The delegated staff completing the eCRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the eCRF.

Data reported on each eCRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete eCRFs will be trained to adhere to the ROSSINI-Platform trial specific working instructions on eCRF completion.

The following guidance applies to data and partial data:

- Time format – all times should be in accordance with the 24hr clock
- Rounding conventions – rounding should be to the nearest appropriate significant figure, in accordance with the CRF: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. Example: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. Example: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

The eCRFs will be considered “complete” once all data fields have been either completed unambiguously or it has been made explicit that the data is unobtainable.

eCRFs submitted outside of the assessment window will not be regarded as protocol deviations.

Data collected by the CDWH will not be queried by the ROSSINI-Platform trial team at the BCTU

12.3 Participant completed questionnaires

Participant completed questionnaires will be collected at:

- Baseline
- Time of discharge review
- Weekly until 30-days post-surgery
    - For those participants with ongoing SSI EQ-5D-5L will continue to be completed monthly until the SSI has resolved or until 120 days post-surgery, whichever is earliest.

Participant completed questionnaires will be completed on paper or electronically at the time of trial entry and discharge from hospital and online post-discharge via the CDWH. Questionnaires should generally be completed by the participant alone, however physical assistance in completing the form can be given by the research staff or the participant’s friends and relatives where appropriate. In such circumstances, questions are to be read to the participant verbatim and responses must not be led by the person assisting with the form completion. This requirement must be made clear when the participant’s friends and relatives are providing the assistance. Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish to by selecting ‘Prefer not to answer’.

12.4 Data Management

The ROSSINI-Platform trial office at the BCTU is responsible for all management of data collected from the point of trial entry until discharge from the index hospital.

Within the BCTU, processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan (DMP) and include the processes of data entry, data queries and self-evident corrections on trial data. Data entry will be completed by the sites via a bespoke BCTU trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

Data collected post-discharge is via the CDWH.

12.5 Self-evident corrections

No self-evident corrections will be permitted.

12.6 Data security

12.6.1 University of Birmingham

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The UoB Trial Database System incorporates the following security countermeasures:

Physical security measures: Servers are virtual machines on central IT infrastructure provided by the University of Birmingham, all three data centres (Aston Webb, Elms Road and Park Grange), have their physical access controlled through the use of the University's standard door access system - Gallagher Cardax.

Rights and permissions are fully granular through the use of groups within the system that can be locked down to both an individual door and specific hours, and are administered by sub-sets of the Data Centre and Building Management Teams. The overarching administration of the system itself is managed by a small number of staff in Estates, Security, and EUS.

This system is fully auditable for access, events, changes, and warnings on any door that is covered by it, with records being held in the system for 12 months.

Logical measures for access control and privilege management: The ROSSINI-Platform web application will use pre-defined system roles to control access to participant data. The administration of Users to these roles is managed by the Trial Management Team.

Network security measures: firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team

System design: the system will comprise of a database and a data entry application with restricted access, and role-based security controls.

Servers: maintained by the University of Birmingham IT services team, who commission routine yearly penetration testing, maintain firewalls and encryption of data at rest.

Operational processes: the data will be processed and stored within the UK campus of the University of Birmingham.

System audit: The system benefits from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

12.6.2 CDWH/Isla

Cloud storage is used with data stored within the UK (Google Firebase cloud storage, hosted in Europe-West-2 (London)) and data is passed to and from the Health Sector via a Health and Social Care Network (HSCN) connection.

Data is sent to Isla cloud storage via the internet over Hypertext Transfer Protocol Secure (HTTPS), and then encrypted in line with Google Firebase server side encryption standards. When participants or staff members submit participant information directly from personal phones, identifiable data is never stored on their devices and is sent to Isla's cloud services via HTTPS. Isla then maintains server-side encryption at the point of storage of any participant data.

Data will be processed by Isla. Isla uses two 3rd party processors, which comply with GDPR requirements, to support the delivery of its service:

- Google Cloud Platform:
  - The cloud storage provider used for the storage of patient data
- Vonage:
  - The SMS provider used by Isla. Note, only the participant phone number and first name are shared with Vonage (the minimum to deliver the service effectively)
  - Note: Vonage can't commit to keeping data within the UK as they require global network coverage to send SMS messages. Only a minimum data set is shared with Vonage, and it is redacted once the processing is complete.
- Sparkpost:
  - The email provider used by Isla
- Cutt.ly:
  - The link shortening platform used by Isla
  - No personal data is shared with cutt.ly
- Intercom:
  The support widget used by Isla to provide support to participants and clinicians
  - No patient data is shared with Intercom by default.

Isla is 100% compliant with the NHS Digital DSP toolkit and is Cyber-Essentials+ accredited, these measures cover a wide array of organisational and technical measures to ensure data is handled appropriately, from encryption standards and network protections through to organisation measures like policies and training.

The Isla Data Protection Impact Assessment (DPIA) is available for review on the Isla website. Privacy-policy - Isla Health (https://isla.health/privacy-policy/)

12.6.3 UCL-MRC

Data will be shared with UCL-MRC as they will undertake a second independent analysis on the data as a sense and accuracy check. Data that will be shared with the UCL–MRC will be held in an access restricted folder within UCL-MRC file store. All servers are virtual servers hosted within the UCL-

MRC virtual server estate. The system is hosted in data centres located in London, UK, which are owned and operated by the UCL-MRC IT Services department.

12.7 Archiving

All records created by following trial procedures and all documents listed in guidance relating to the conduct of the trial must be retained and archived for the specified period.

The trial master file is normally composed of a sponsor file, held by the UoB as the sponsor organisation, and an investigator site file, held by the local PI at each participating site. Documents are archived following regulatory requirements and any local procedures.

Retained data should still be accurate, accessible & stored securely and confidentially.

It is the responsibility of the local PI and site pillar leads to ensure all essential trial documentation and source documents (e.g., signed ICFs, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Site set-up and initiation

Each hospital participating in ROSSINI-Platform must identify a Local PI who takes overall responsibility at the site for the Platform. Each Pillar that the hospital is participating in must have a Site Pillar Lead; the local PI may also be a Site Pillar Lead.

The PI and all Site Pillar Leads at each hospital site will be asked to sign the necessary agreements including:

- ROSSINI-Platform Site PI to Site Pillar Lead Delegation of Duties log
- Site Pillar Lead Signature and Delegation log between the Pillar Lead and the Trial Office.

All local PIs and Site Pillar Leads, plus other members of staff as deemed appropriate, will be asked to supply a current CV and GCP certificate to the BCTU.

All members of the site research team are required to sign the Site Pillar specific Signature and Delegation Log, which details which tasks have been delegated to them by the Site Pillar Lead. The Site Pillar Specific Signature and Delegation Log should be kept up to date by the Pillar Lead.

It is the Local PIs responsibility to inform the Trial Office of any Site Pillar Lead changes, and it is the Site Pillar Lead responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation; site initiation will be pillar-specific and will be either via a meeting or a video-conference. The site pillar lead (who may also be the local PI) plus key members of the site research team are required to attend the site initiation visit (SIV), which will cover the trial design and both the generic and pillar-specific aspects of protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

13.2 Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

13.2.1 On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the ROSSINI-Platform trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

13.2.2 Central monitoring

The Trial Office will check received ICFs and eCRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the DMP. Sites will be sent queries raised via the trial database requesting missing data or clarification of inconsistencies or discrepancies.

13.3 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

13.4 Notification of Serious breaches

In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial, within 7 days of becoming aware of that breach. For the purposes of this regulation, a “serious breach” is a breach which is likely to affect:

- the safety or physical or mental integrity of the participants of the trial

- the scientific value of the trial.

Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

14. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of data queries. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC, MHRA and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the MHRA and REC within 15 days of the end of trial. The Trial Office will provide the REC, MHRA and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

15. STATISTICAL CONSIDERATIONS

15.1 Sample Size

ROSSINI-Platform uses a basket factorial MAMS design. There are 6 pillars – one each for a different surgical speciality (vascular groin, LLA,, obstetric, breast, neurosurgery, cardiac). Sample sizes are calculated for each of the pillars separately, following the same structure.

There are three interventions for each pillar, which vary over the different pillars. These will be called A, B and C in this section. The factorial design means that the raw control group (i.e. the combination Not A, Not B, Not C) event rates could potentially need to be reduced in situations where more than one of the treatments might be effective. Since the trial is targeting an absolute risk reduction for all pillars, this has been acknowledged, but a conservative approach has been taken where, when testing the hypothesis A vs. not A, then treatments B and C are assumed to be ineffective. The situation would be different (and reversed) if a relative risk reduction was targeted.

At least one interim analysis is incorporated into the design for each pillar where interventions may be dropped, although the power is sufficient for all interventions to reach the end. The number of interim analyses is dependent on the length of time needed for recruitment – at least one, but two where possible.

The rate of recruitment is assumed to be constant within a pillar. No ramp-up has been incorporated.

Table 12 outlines the design specification, stagewise sample sizes and the overall operating characteristics for each pillar:

Table 12 - Design specification, stagewise sample sizes and the overall operating characteristics for each pillar

Design specifications	Vasc. Groin	LLA	Obstetric	Breast	Neurosurgery	Cardiac
Control group event rate	17.5%	21%	8%	5%	5%	4.5%
Target treatment effect (absolute effect reduction)	4%	5%	2%	2%	2%	2%
Number of stages	3	3	2	2	3	2
Design power at each stage	0.95, 0.95, 0.90	0.95, 0.95, 0.90	0.95, 0.90	0.95, 0.90	0.95, 0.95, 0.90	0.95, 0.90
Significance level at each interim* stage (one-sided)**	0.40, 0.20	0.40, 0.20	0.35	0.35	0.40, 0.20	0.35
Maximum event rate for each intervention to continue	17.0% 16.1%	20.3% 19.3%	7.6%	4.6%	4.7% 4.3%	4.1%
Final stage efficacy boundary (onesided, P-value<)	0.025	0.025	0.025	0.025	0.025	0.025
Recruitment/month in each stage	80	50	1000	300	140	400
Sample size at each stage (cumulative)***	1252, 2146, 3648	922, 1580, 2686	2852, 7266	1678, 4280	1468, 2520, 4280	1476, 3764
Duration of each stage (months, cumulative)	16, 27, 46	19, 32, 54	3, 8	6, 15	11, 18, 31	4, 10
Overall power	0.86	0.86	0.87	0.87	0.86	0.87
Overall type I error rate **	0.025	0.025	0.025	0.025	0.025	0.025

* at each interim stage, this is a guideline value to stop further randomisations to a specific intervention.

** all significance levels and the overall type I error rates are one-sided for each intervention.

*** all figures assume 6% loss to follow-up.

The justification for the sample size is based on a cross-pillar generic ARR strategy linked to the control arm SSI risk, which was considered the most useful and appropriate, as shown in Table 13. This design resulted in effect sizes in each pillar which would be sufficient to persuade surgeons to change their practice.

Table 13 - Baseline risks of SSI event between pillars and target absolute risk reduction

Baseline SSI rate	Target ARR
<10%	2%
10.1 - 15%	3%
15.1 - 20%	4%
20.1 - 25%	5%

The overall type I error rate and power

The overall type I error rate for each intervention is strongly controlled at the (one-sided) 0.025 level in all pillars.

The overall power to detect the target effect size for each intervention is 0.87 in the 2-stage designs (obstetric, breast, cardiac) across all pillars. For 3-stage designs (Vascular Groin, LLA, neurosurgery), the overall power decreases slightly to 0.86 due to the additional interim lack-of-benefit analysis, but it is still at a relatively high level to detect the target effect sizes.

Loss to follow-up

It is assumed that 6% of patients will be lost to follow-up or the primary outcome evaluation will be missing, e.g. surgery not undertaken. This is based on the real-world rates seen in the current ROSSINI 2 trial.

Recruitment assumptions

The projected rates of recruitment are based on the overall annual population pool of eligible operations, alongside hospital opening predictions and suitably conservative estimates of the proportion of eligible cases at a site open for the trial pillar which will be tangibly recruited.

15.2 Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses in each pillar. A brief outline of the planned analyses is given below.

As this is a factorial design, participants will be randomised using separate randomisation schedules (CRCs) and in a 1:1 ratio separately for each of the three interventions (e.g. “intervention A” vs not “intervention A"), and may therefore be allocated to receive any combination of 0, 1, 2 or all 3 of the interventions available in a pillar. For each intervention the comparison will be between 1) the combinations that include the intervention, and 2) the combinations which do not include the intervention. The effect for each intervention will be calculated from the full factorial design, adjusting for important prognostic factors and minimisation variables where possible. This will include a categorical variable indicating the randomisation schedule from which each participant was randomised, and three binary variables, one for each intervention. As the trial is evaluating 3

distinct interventions in each pillar, there is no need to adjust the type I error rate for the fact that 3 primary comparisons are being made in each pillar.

Each end-of-stage analysis will be carried out when sufficient participants, as specified by the required stagewise sample sizes, have contributed data to the primary outcome analysis. After each interim analysis, the DMEC will review confidential data and will make a recommendation to the TSC, who will make the final decision about continuing and/or stopping recruitment to individual interventions.

The comparison between the combination groups will be evaluated using the absolute difference in the proportion of participants reporting SSI within 30 days of surgery. The percentage of participants who have no data on primary outcome measure (because they are e.g. lost to follow-up, or died following the operation) will be monitored closely for its potential impact on the estimated difference. Participants who are randomised but do not undergo surgery will be excluded from the analysis and will not be followed up. We anticipate that this number will be negligible, as randomisation will take place around the time of anaesthetic induction on the day of surgery.

15.2.1 Primary outcome

The primary outcome measure is the proportion of participants undergoing surgery who report SSI within 30 days of surgery, as defined in section 9.2.1, which will be used as the outcome measure at both the interim and the final analyses. This outcome is a binary outcome (i.e. yes/no). The number and percentage of participants experiencing SSI within 30 days of surgery will be reported. An adjusted absolute risk difference and adjusted relative risk ratio, and the associated 95% confidence intervals, will be estimated from a logistic regression model using the binomial distribution and logit link (with robust standard error), followed by marginal standardisation. The p-values from the associated test statistic will be produced and used to determine statistical significance for both risk difference and risk ratio, but the p-value generated by the model estimating the absolute risk difference will be used for decision making, as the sample sizes were calculated using absolute differences.

15.2.2 Secondary outcomes

Binary Outcomes (e.g., hospital re-admission for wound related complications within 30 and 90 days post-surgery; occurrence of wound reopening and/or re-operations within 30 and 90 days post-surgery; wound or intervention only related SAEs up to 90 days).

The secondary outcomes that are binary (i.e., yes/no) will be analysed using the same methods as described for the primary outcome (see Section 15.2.1), with corresponding 95% confidence intervals.

Time to Event Outcomes (e.g., length of hospital stay; 30-day POMR) will be compared using standard survival analysis methods. Kaplan-Meier survival curves will be constructed for visual

presentation of time-to-event comparisons. Cox proportional hazard models will be fitted to obtain adjusted treatment effects which will be expressed as hazard ratios with 95% confidence intervals.

Continuous Outcome assessed repeatedly (i.e., EQ-5D-5L) will be analysed using mixed effects linear regression methods for repeated measures to calculate an adjusted mean difference between groups in both EQ-5D-5L index score and EQ-VAS score, along with the 95% confidence intervals. Assessment time point will be included as a categorical variable, and the interaction between treatment group and time will be included in the model as fixed effects. Participant will be included as a random effect to account for the repeated measures of the scores.

Ordinal Outcomes (i.e., 30-day postoperative worst wound complication) will be analysed using a mixed effects ordinal regression model to estimate the adjusted odds ratio with the 95% confidence interval.

Other Outcomes (i.e., cost effectiveness (Resource Use Questionnaire; RUQ))

These outcomes are part of the health economic analysis and are included in the analysis presented in Section 16.

15.2.3 Planned subgroup analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (see PSPs)) and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. Subgroup analysis will be reported separately for each intervention. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

15.2.4 Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include the 'tipping point' scenario[36].

Further sensitivity analysis will include an analysis of the adherence to each intervention separately and overall.

Full details will be included in the SAP.

15.3 Planned interim analysis

The formal interim analyses will include efficacy data alongside other important aspects such as adherence and acceptability, to enable the DMEC to determine which arms to recommend being dropped. The Vascular Groin, LLA, and Neurosurgery pillars will have three stages of analysis (two interim and one final), whereas the Obstetric, Breast, and Cardiac pillars will have two.

In a design with two analyses, the observed one-sided P-value at the first interim analysis will be compared against the stage 1 significance level of 0.35.

If the observed P-value is larger than 0.35, the DMEC can recommend the dropping of the intervention for lack-of-benefit. Table 12 in section 15.1 includes the corresponding threshold on the treatment effect size scale. For example, in the Obstetric pillar, if the difference in observed risk (intervention – control) is larger than 7.6% - 8.0% = -0.4%, the intervention can be considered to be dropped for lack-of-benefit.

In 3-stage designs, the observed P-values at stages 1 and 2 will be compared against the corresponding stagewise significance levels of 0.40 and 0.20. If the observed P-values are larger than the corresponding significance levels at either of the stages, the DMEC can consider recommending the dropping of the intervention for lack-of-benefit.

For the interim analyses, once the target number of patients is recruited, it is expected that around 2-3 months will pass until the decision time regarding stopping and/or continuing any intervention. This is to allow for 30-day follow-up to obtain primary outcome data, the recording of data in the database, the undertaking of the interim analysis, and then DMEC & TSC meetings to be held.

15.4 Planned final analysis

The primary analysis for the trial will occur once all participants have completed the 90-day assessment, the corresponding outcome data has been entered into the trial database and validated as being ready for analysis. This analysis will include data items up to and including 120 days post-surgery, to allow for resolution of ongoing SSIs, and no further.

16. HEALTH ECONOMICS

A separate Health Economics Analysis Plan (HEAP) will be produced and will provide a more comprehensive description of the planned analyses. A brief outline of these analyses is given below.

A cost-utility analysis will be undertaken to determine the cost-effectiveness of the compared interventions. The base case analysis will adopt an NHS and personal social services perspective.

Resource use and costs: Resource use will be collected alongside the proposed trial through CRFs and patient questionnaires. These will include : i) costs associated with the purchase and use of the in-theatre interventions under assessment, ii) postoperative secondary care resource use (e.g. inpatient stay, outpatient appointments, additional procedures and investigations, antibiotics usage), iii) post-discharge primary care resource use (GP consultations, nurse appointments, medication provided in the community). Resource use will be valued by unit costs taken from up-

to-date national sources, including the Unit Costs of Health and Social Care, the British National Formulary (BNF) and the NHS Reference Cost Schedules.

Outcomes: The main outcome measure in the cost-utility analysis will be the Quality-Adjusted Life Years QALY which will be estimated through patients' responses to the EQ-5D-5L instrument at baseline, on discharge, then weekly (via the CDWH/Isla through to the final normal review at 30-33 days post-surgery. If a patient is diagnosed with SSI and the effects of this are still ongoing beyond 30 days, we will ask their permission to continue to remotely collect monthly EQ-5D-5L scores beyond this point until resolution (to a maximum of 120 days), to ascertain the impact of an ongoing SSI. With their permission, we will also collect monthly EQ-5D-5L scores from a subsection of patients without an SSI to serve as a comparator for the patients with ongoing SSI. Each patient's health status descriptions obtained from the EQ-5D-5L will be translated into a single, preference-based (utility) index using a UK specific value set. QALYs will be estimated for each participant using the area under the curve approach.

Analysis: Given the nature and time frame of the clinical question, relevant costs and outcomes are expected to be largely captured within the study follow-up period. Thus, the main analysis will be carried out on the basis of patient- level data obtained within the study follow-up period. Data will be analysed on an 'intention to treat' basis. Missing data will be accounted for using multiple imputation techniques, depending on the extent and type of missing items. As the distribution of cost is usually skewed, the calculated mean per-patient cost will be given alongside confidence intervals obtained through non-parametric bootstrap methods. Incremental analysis will be undertaken to calculate the difference in costs and QALYs associated with each of the interventions. Results will be presented in the form of incremental cost-effectiveness ratios (ICER), reflecting the extra cost for an additional QALY. To account for the inherent uncertainty due to sampling variation, the joint distribution of differences in cost and QALYs will be derived by carrying out 5,000 non-parametric bootstrap simulations. The simulated cost and QALY pairs will be depicted on a cost-effectiveness plane and will be plotted as cost-effectiveness acceptability curves (CEACs).

CEACs will show the probability of each intervention being cost-effective across a range of possible values of willingness to pay for an additional QALY.

17. SUB-STUDIES

There are no sub-studies within this trial within initial phase.

18. TRIAL ORGANSATIONAL STRUCTURE

18.1 Sponsor

The University of Birmingham is the sponsor for this trial. It takes overall responsibility for initiation, management and financing of the trial.

18.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at the UoB.

ROSSINI-Platform involves close interaction between BCTU and the MRC CTU. The MRC CTU are experts in MAMS trial design and analysis. As well as providing ongoing input into the design and conduct of the trial, they will oversee the statistical team at BCTU in undertaking the data analysis.

18.3 Executive Trial Management Group

The Executive Trial Management Group (ETMG), which comprises all members of the co-applicant group, will review progress, troubleshoot and plan strategically. The ETMG includes: the CI, the co-lead of the ETMG, Pillar Leads, Pillar Deputy Leads, statistician(s), programme manager, trial management team leader, trial managers, health economist(s), patient representative(s) and PPI manager. The role of the group is to monitor all aspects of the conduct and progress of the trial from a platform level, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The ETMG will meet sufficiently frequently to fulfil its function.

18.4 Pillar TMGs

Each pillar will have a Pillar-specific Trial Management Group – the Pillar TMG, which comprises individuals responsible for the day-today management of the pillar-specific elements of the trial. This will include the Platform Pillar Lead, Platform Deputy Pillar Lead, trial managers, clinical research practitioner, statistician, representative from BCTU trial team and a patient representative. The role of the Pillar TMG is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. Any issues can be escalated up to the ETMG. Meetings will be held as required, but at least 6 times per year.

18.5 Public and Patient Involvement Group

The ROSSINI-Platform includes a ‘Core’ Public and Patient Involvement (PPI) group as well as dedicated Pillar-specific PPI groups. The core PPI group is led by two experienced PPI leads (a PPI officer and a patient co-applicant) and supported by a PPI manager. The core group is responsible for the overall PPI strategy for the platform as well as core PPI dissemination and outputs. The core group also consists of the pillar PPI leads, members of the UoB ROSSINI-Platform team, plus individual patient representatives coming from each pillar.

Each pillar-specific PPI groups is responsible for pillar-specific issues, including, but not limited to, consent/assent pathways, communication strategies to individual patient groups, input into intervention selection and results dissemination. It is composed of the pillar PPI lead (member of staff) and 8-12 patient representatives and/or carers.

18.6 The Associate Principal Investigator Scheme

At least one associate principal investigator (API) per surgical pillar will be permitted at each site. Multiple APIs per site are permitted but must commit to completion of their six-month minimum tenure and achieving formal API sign-off by the NIHR co-ordinating centre. The Associate PI will undertake a variety of defined roles including: supporting trial approvals, co-ordinating within team communication, patient recruitment and onboarding to Isla, follow-up at 30/90 days, co-ordination of other trial team members and support of BCTU to ensure that all members of the trial team have completed mandatory training and signed the delegation log. For more information on the Associate PI scheme please see:

associate-principal-investigator-scheme

18.7 Trial Steering Committee

A TSC comprising independent and non-independent members, will be established for the ROSSSINI-Platform trial and will meet via video-conference or face-to-face, as required depending on the needs of the trial and/or at the request of the DMEC to coincide with the timing of any interim analyses. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight and overall supervision of the trial, including the practical aspects of the trial. Membership of the TSC is listed at the front of the protocol. The TSC will monitor trial progress and conduct and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMEC and ultimately carries the responsibility for deciding whether the trial, or arms of the trial need to be stopped on grounds of safety or efficacy

18.8 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants or if there are any ethical or safety reasons as to why the trial should not continue ‘as is’ or whether it needs to be modified.

The DMEC will operate in accordance with a trial specific ROSSINI-Platform DMC charter based upon the template created by the Damocles Group. The DMEC will meet at the interim analysis time points unless there is a specific reason (e.g. safety) to amend the schedule.

Given the complexity of this trial and the variability in timing for the requirement for interim analysis across pillars, additional meetings may be called if recruitment varies in pace to that anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment.

An emergency meeting may also be convened if a safety issue is identified.

The DMC will report directly to the TSC who will convey the findings of the DMC to the ETMG and/or the REC or funders as required. The DMC may consider recommending the discontinuation of the trial or intervention if the recruitment rate or data quality are unacceptable or if any issues are

identified which may compromise participant safety. There are no formal rules for stopping the trial or an intervention, in the situation where there is evidence of treatment benefit, and any decision to make such a recommendation would be at the DMEC's discretion.

18.9 Finances

The research costs of the trial are funded by the NIHR Health Technology Assessment (HTA) programme awarded to Professor Thomas Pinkney at the UoB. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess treatment costs (ETCs) associated with the trial, e.g. gaining consent, are estimated in the Schedule of Events Cost Attribution Template (SoECAT). ETC costs should be met by accessing the Trust's Support for Science budget via the Research Delivery Network (RDN), service support costs are funded through the usual commissioning processes for patient care.

19. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include, but are not limited to, the Medicines for Human Use (Clinical Trials) 2004, Data Protection Act 2018, and the Mental Capacity Act 2005. This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations and according to the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the MHRA and/or REC will be retained in the TMF/ISF. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the Local PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

20. DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data (including that of carers/ family members supporting participants) recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Personal data categories that will be collected include name, NHS/CHI/H&C Number, gender, date

of birth, telephone/mobile number, email and postal address, health information and medical history.

Participants will only be identified by their unique trial identification number on any correspondence with the Trial Office and participating site. Participants will acknowledge the transfer and storage of their ICF to the Trial Office; this will be conducted as part of the consent process. This will be used to perform central monitoring of the consent process.

Participants will acknowledge the transfer of their personal data for the purpose of medical research to and analysis to the University of Birmingham, the CDWH at GSTT and UCL-MRC who will be processing the data on behalf of the trial.

BCTU, GSTT and MRC will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the ROSSINI-Platform team and Sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. All appropriate data access restrictions will be in place to ensure that data access is necessary and proportional to carry out the analysis required.

21. FINANCIAL AND OTHER COMPETING INTERESTS

ROSSINI-Platform is an investigator-initiated and investigator-led trial funded by the NIHR HTA Programme. All interventions, including training are provided free-of charge by the intervention suppliers. The trial design, data collection, analyses and interpretation of the findings remain under control of the ETMG.

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMEC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

22. INSURANCE AND INDEMNITY

The University of Birmingham (UoB) has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at The University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority. The UoB is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

23. POST TRIAL CARE

At the end of the trial, all participants will continue to receive standard care as provided by the NHS following participation in the clinical trial, and as deemed appropriate by their responsible clinician and usual clinical care team.

24. ACCESS TO FINAL DATA SET

The final dataset will be available to members of the ETMG and others who need access to the data to undertake the final analyses. This will include staff at both UoB and the UCL-MRC.

Requests for data generated during this study will be considered by BCTU. Data will typically be available six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

25. PUBLICATION PLAN

On completion of a pillar of the trial, the data will be analysed, and a Pillar specific Study Report prepared. Results will be submitted for publication in a peer reviewed journal and the findings will be made public. This manuscript will be prepared by the pillar TMG in conjunction with the CI and members of the ETMG.

Outputs from this trial will be published under a corporate authorship group. Each publication will include a detailed description of the exact contributions of each person, following accepted guidelines for collaborative authorship models.

Any secondary publications and presentations prepared by investigators must be reviewed and approved the ETMG. Manuscripts should be submitted to the ETMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues.

In all publications, authors must acknowledge that the trial was performed with the support of NIHR, the UoB (the Sponsor) and BCTU. Intellectual property rights will be addressed in the ROSSINI-Platform Clinical Trial Site Agreement between Sponsor and site.

Participants can request the published trial results from their Local PI once available.

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APPENDIX 1

The list below is the Hierarchical list of potential Nearest Relatives as defined in section 26 of the Mental Health Act 1983

Hierarchical list of potential nearest relatives

1. Husband or wife or civil partner (except one permanently separated from the patient by agreement or a court order, or who has deserted or been deserted by the patient)
2. Person who qualifies as a relative by living with the patient as husband or wife or as if they were civil partners for at least six months (ie person treated as a husband, wife or civil partner under the Act)
3. Son or daughter aged 18+
4. Father or mother
5. Brother or sister aged 18+
6. Half-brother or half-sister aged 18+
7. Grandparent
8. Grandchild aged 18+
9. Uncle or aunt aged 18+ of the whole blood
10. Uncle or aunt aged 18+ of the half-blood (e.g. half-sister of patient's mother)
11. Nephew or niece aged 18+ of the whole blood
12. Nephew or niece aged 18+ of the half-blood (i.e. child of a half-brother of the parent of the patient)
13. Other person aged 18+ who qualifies as a relative by having lived with the patient for at least five years

Note: Includes relationships made through adoption. Excludes step relationships. Also excludes the relationship of a father and a child under 18 who is not born to parents who are married or in a civil partnership and any relationship established through such a relationship, e.g. between aunt and nephew, unless the father has parental responsibility for the child.