ROSSINI-PLATFORM TRIAL

Pillar-Specific Protocol

BREAST

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**

BREAST PILLAR SPECIFIC PROTOCOL DEVELOPMENT

Protocol amendments

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

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

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

SUPPLIERS	
ESSITY	Provision of intervention
MOLNLYCKE	Provision of intervention

PROTOCOL SIGN OFF

Pillar Lead for Breast - Signature Page

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

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

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

Trial name:	ROSSINI-PLATFORM (BREAST Pillar)
Protocol version number:	Version: __ __
Protocol version date:	__ __ /__ __ __ /__ __ __ __
Pillar Lead name:	Miss Katherine Fairhurst
Signature and date:	_____ __ __ /__ __ __ /__ __ __ __

Sponsor statement

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

Compliance statement

This protocol describes the BREAST Pillar within the ROSSINI-Platform trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the BREAST Pillar of the ROSSINI-Platform trial.

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

Principal Investigator (PI) signature page

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

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

Trial name:	ROSSINI-PLATFORM (BREAST Pillar)
Protocol version number:	Version: __ __
Protocol version date:	__ __ /__ __ __ /__ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __ /__ __ __ /__ __ __ __

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Trial website	< tbc >
Trial social media	< tbc >

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TBC	Patient and Public Representative

ABBREVIATIONS

Abbreviation	Term
ABS	UK Association of Breast Surgery
ARR	Absolute Risk Reduction
ASA	American Society of Anesthesiologists
BCTU	Birmingham Clinical Trials Unit
BMI	Body Mass Index
CDC	Centre for Disease Control
CDWH	Centralised Digital Wound Hub
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
DACC	Dialkylcarbomoyl chloride
eCRF	Electronic Case Report Form
ETMG	Executive Trial Management Group
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	NIHR Health Technology Assessment scheme
ISF	Investigator Site File
IV	Intravenous
MAMS	Multi Arm Multi Stage
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPWT	Negative Pressure Wound Therapy
NSQIP	National Surgical Quality Improvement Program

PAUS	Prophylactic Antibiotic Use in Surgery
PI	Principal Investigator
PSP	Pillar-Specific Protocols
RCT	Randomised Controlled Trial
RAG	Red-Amber-Green
REC	Research Ethics Committee
RR	Relative Risk
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSI	Surgical Site Infection
SOP	Standard Operating Procedure
TLR	Toll-like receptors
TSC	Trial Steering Committee
UK	United Kingdom

ROSSINI PLATFORM: BREAST PILLAR TRIAL SUMMARY

INTERVENTIONS	**Intervention 1:** Prophylactic antibiotics at induction **Intervention 2:** Wound irrigation with Granudacyn® prior to closure **Intervention 3:** Dialkylcarbomoyl chloride (DACC)-coated dressings
PARTICIPANT POPULATION AND SAMPLE SIZE	**Participant Population** = approx. 45,000 operations each year in the UK. • If 80% patients are eligible across 50% of sites = 18,000/year. • Recruitment rate of 30% = 22,500 recruitable patients over 50 months. **Sample size calculation;** • 5% baseline SSI rate, with 2% ARR = sample size 4,280
PILLAR-SPECIFIC ELIGIBILITY CRITERIA **INCLUSIONS**	• Patients aged 18 and over • Patients undergoing resectional surgery for breast cancer, including breast conservation surgery, mastectomy, oncoplastic surgery and axillary surgery. • Patients able to provide informed consent
PILLAR-SPECIFIC ELIGIBILITY CRITERIA **EXCLUSIONS**	• Patients undergoing breast surgery for breast cancer with whole breast reconstruction (i.e. implant reconstruction or autologous free flap reconstruction) • Patients undergoing a re-excision of margins for cancer. • Patients with a known allergy to any of the interventions: • For intervention 1: **Prophylactic antibiotics at induction** ○ Known allergy to any of the antibiotics used within the breast pillar • For intervention 2: **Wound irrigation with Granudacyn® prior to closure** ○ Known allergy to any of the ingredients contained in Granudacyn® • For intervention 3: **Dialkylcarbomoyl chloride (DACC)-coated dressings** ○ Known allergy to dialkylcarbomoyl chloride (DACC)-coated dressings
RECRUITMENT TARGETS	4,280 participants
TIMELINES	Up to 50 months of recruitment

TRIAL SCHEMA

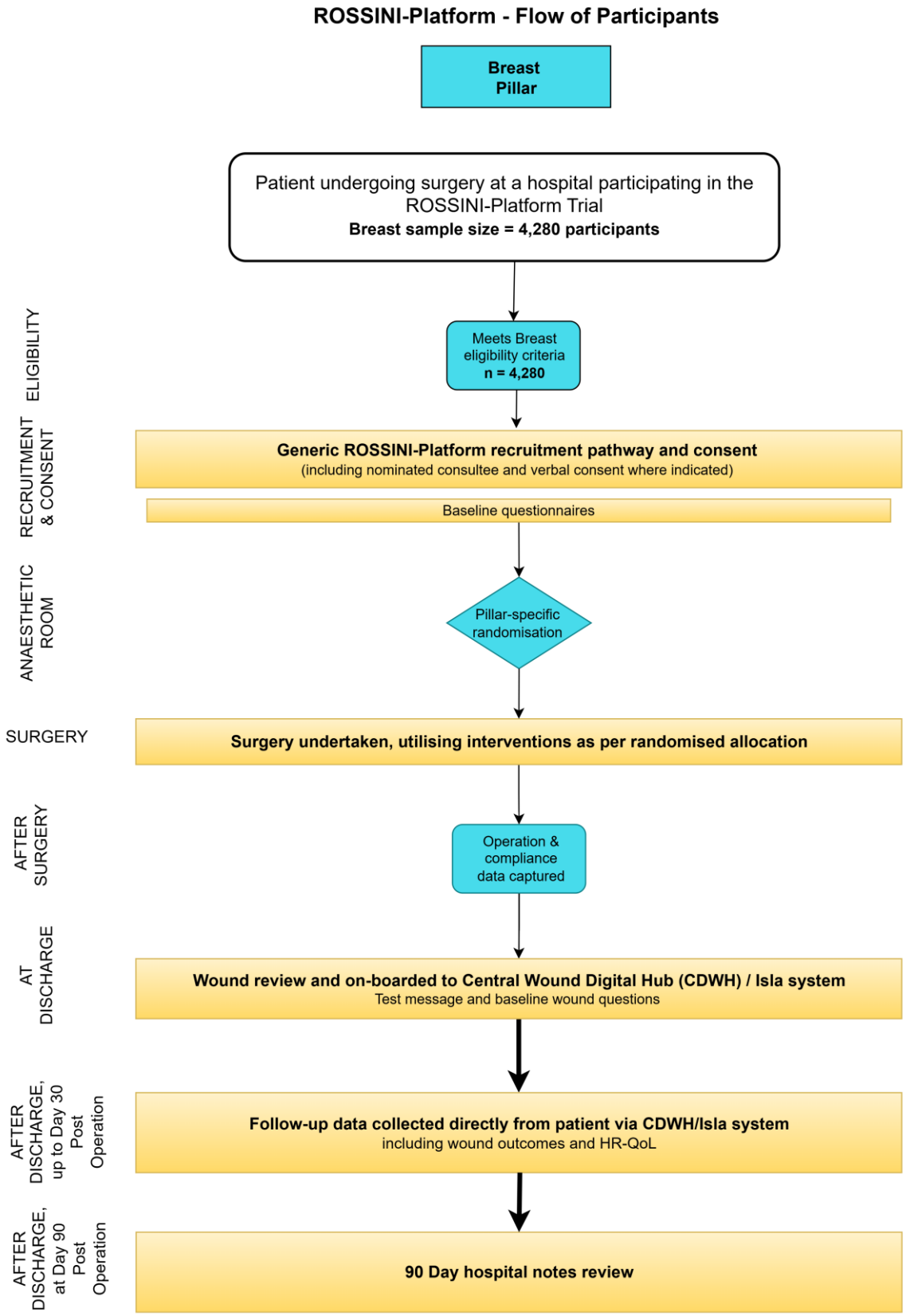
ROSSINI-Platform - Flow of Participants
Breast Pillar
Patient undergoing surgery at a hospital participating in the ROSSINI-Platform Trial
Breast sample size = 4,280 participants
ELIGIBILITY
Meets Breast eligibility criteria n = 4,280
RECRUITMENT & CONSENT
Generic ROSSINI-Platform recruitment pathway and consent
(including nominated consultee and verbal consent where indicated)
Baseline questionnaires
ANAESTHETIC ROOM
Pillar-specific randomisation
SURGERY
Surgery undertaken, utilising interventions as per randomised allocation
AFTER SURGERY
Operation & compliance data captured
AT DISCHARGE
Wound review and on-boarded to Central Wound Digital Hub (CDWH) / Isla system
Test message and baseline wound questions
AFTER DISCHARGE, up to Day 30 Post Operation
Follow-up data collected directly from patient via CDWH/Isla system
including wound outcomes and HR-QoL
AFTER DISCHARGE, at Day 90 Post Operation
90 Day hospital notes review

TABLE OF CONTENTS

1. PILLAR SPECIFIC PROTOCOL STRUCTURE

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

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

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

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

2. BACKGROUND AND RATIONALE

2.1 Pillar definition

This is a Pillar within the ROSSINI-Platform Trial to test the effectiveness of specific peri-operative interventions to prevent surgical site infection (SSI) in adult patients undergoing resectional surgery for breast cancer.

2.2 Pillar-specific background

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases, and almost 57,000 new cases every year (1). Around 90% of breast cancers will be treated with surgery, and 76% of people diagnosed with breast cancer will survive 10 years or more (2). As most breast cancer patients survive a long-time following treatment, patient experience as well as a

variety of outcomes including cosmesis, quality of life and oncological outcomes such as recurrence, are very important.

SSI after breast surgery can profoundly impact both patient outcomes and experience (3). For those affected, the impact of SSI can range from readmission for IV antibiotics, prolonged dressing management, to further surgery for washout and drainage, with associated additional hospital visits which can be distressing and costly. Furthermore, infection adversely impacts cosmetic outcomes after breast surgery which can dramatically affect quality of life and long-term wellbeing. Finally, SSIs may delay delivery of adjuvant therapies such as chemotherapy (4) and/or radiotherapy (5), which may adversely impact oncological outcomes and there is some evidence that SSIs may increase the risk of breast cancer recurrence (6). The mechanism for this is not fully understood, but surgical complications are thought to prolong the inflammatory, angiogenic and immunosuppressive effects of surgical stress and tissue trauma (7), which create a prometastatic environment. The adhesion and survival of circulating tumour cells through the activation of toll-like receptors (TLRs) may also be enhanced by post operative infection, further promoting metastatic spread (8).

Breast surgery wounds are classified as “clean” with the 1985 Center for Disease Control’s (CDC) guidelines reporting estimated SSI rates of between 1-5% (9). In the literature the reported SSI rates in breast surgery vary widely from 2.1% to 21% (3, 10-14). Published US data from the National Surgical Quality Improvement Program (NSQIP) of over 54,000 women undergoing breast cancer surgery in 2012-2015 demonstrated an SSI rate of 2.1%, with risk factors for SSI including mastectomy, diabetes, smoking, COPD, ASA class-severe, BMI >35 kg/m^2, and a length of stay of more than one day (3). A retrospective cohort analysis of 50,000 patients undergoing surgery published in 2023, used the Clinical Practice Research Datalink database linked with secondary care datasets generated by Hospital Episode Statistics, to characterise SSI rates in UK NHS practice (15). This demonstrated an SSI rate of 10% for breast surgery in the UK (n=403 patients) with a mean time to SSI onset of 16.2+/-11.2 days. The vast majority of these SSIs occurred after discharge from hospital (approx. 90%) meaning SSI incidence in breast surgery may have been historically underestimated.

The Breast Pillar of the ROSSINI-Platform Trial intends to evaluate the effectiveness of three interventions to reduce SSI in adult patients undergoing resectional surgery for breast cancer in the UK. Given the heterogeneity of SSI rates identified in the literature, a conservative SSI rate of 5% has been selected for this pillar, with an absolute risk reduction of 2% in the intervention arm.

2.3 Pillar-specific rationale

There are multiple interventions currently used to reduce SSI rates in surgery. In breast surgery specifically, few are underpinned by high quality evidence. Consequently, there is wide variation in practice across the UK regarding commonly used SSI reduction measures, for example, the use of antibiotics, wound washing and different types of dressing, including the utilisation of negative pressure wound therapy (NPWT). As part of the feasibility work for this trial, we surveyed UK breast surgeons which demonstrated huge variation in practice, with 72% stating more evidence was required to help reduce SSI in breast surgery and 75% felt that dressings may have a role in reducing SSI. All interventions have potential side effects and costs, so it is important that those interventions utilised are proven to be effective at reducing SSI, are cost-effective and acceptable to patients and the NHS.

2.3.1 Justification for pillar-specific participant population

All adult patients undergoing resectional surgery for breast cancer, including breast conservation surgery, mastectomy, oncoplastic surgery (including therapeutic mammaplasty and chest wall perforator flaps) and axillary surgery with be eligible for inclusion in the Breast Pillar of the ROSSINI-Platform Trial.

Patients undergoing whole breast reconstruction with either implants or autologous tissue are excluded. Autologous breast reconstruction is almost exclusively performed by plastic surgeons in the UK, and in specialised centres only. Given that these procedures are performed by a separate surgical speciality, it would not be feasible to include them in the breast surgery pillar.

Patients undergoing implant-based breast reconstruction will also be excluded. This is because SSI rates in these patients are high (approximately 25%)(16) and UK surgeons are not in equipoise regarding interventions to reduce SSI in this patient group. Many surgeons use infection prevention bundles including the Manchester Theatre Implant Checklist list (17) or the Exeter Checklist (18) and would not be willing to randomise patients undergoing implant surgery to interventions in the trial.

2.3.2 Justification for choice of interventions

Intervention 1: Prophylactic antibiotics at induction

A Cochrane review update in 2019 (10) concluded that prophylactic antibiotics probably reduce the risk of SSI in breast surgery, but commented that the included studies were extremely heterogenous, and highlighted the need for further large scale RCTs in this area.

The multicentre PAUS trial (Prophylactic Antibiotic Use in Surgery, n=871) randomised patients undergoing breast surgery to IV antibiotics vs no antibiotics (12). This study suggested a lower rate

of SSI in patients receiving IV co-amoxiclav at induction compared with those who did not receive antibiotics however, this difference was not statistically significant (16.2% vs 19.2%, OR 0.82, 95% CI 0.58 to 1.15, p=0.25). The SSI rates reported in this trial are higher than would be anticipated. This may reflect the fact that although this study was only published in 2022, participants were recruited over 20 years ago (2002-2005), when rates of patient colonisation with *Staphylococcus aureus* were higher and infection control practices may have been substantially different.

Current guidelines from the National Institute for Health and Care Excellence (NICE) (19) and the UK Association of Breast Surgery (ABS) (20) recommend that surgeons should 'consider' a single dose of antibiotics for all breast cancer surgery, but these guidelines have not been widely adopted due to the lack of high-quality evidence supporting them. Practice therefore varies widely even within individual breast surgical units.

Intervention 2: Wound irrigation with Granudacyn® prior to closure

There are no studies evaluating the use of wound wash in breast cancer surgery and practice varies significantly (wash/no wash and type of wash used) across the UK. Wound cleansing with Granudacyn® (a pH-neutral hypotonic wound cleansing solution containing hypochlorous acid) facilitates the mechanical removal of microorganisms and cell debris and has been shown to be effective at improving healing in chronic wounds such as diabetic foot ulcers, leg ulcers and pressure sores (21-25), as well as in more acute wounds such as burns and skin grafts (26, 27). RCTs of hypochlorous acid containing wound irrigation solutions to reduce SSI have been conducted in other clinical areas including acute peritonitis (28) and sternotomy wounds (29). Most recently, a large systematic review and meta-analysis demonstrated that prophylactic wound irrigation with antiseptic solutions was highly effective at reducing SSI in all types of surgery compared to no irrigation (RR, 0.60; 95% CI, 0.44-0.81; high level of certainty) and more effective than antibiotic solutions (RR, 0.46; 95% CI, 0.29-0.73; low level of certainty). Saline irrigation showed no statistically significant difference compared with no irrigation at reducing SSI (RR, 0.83; 95% CI, 0.63-1.09; moderate level of certainty). This review suggested that the use of antibiotic wound irrigation be avoided due to the inferior certainty of evidence for its outcome and global antimicrobial resistance concerns (30).

Whilst breast surgery is 'clean surgery', many of the incisions are peri-areolar or axillary which are areas known to carry a higher skin flora burden, and may contribute the higher incidence of wound infection than may be expected with clean surgery (9). In addition, many breast surgeons irrigate the wound prior to closure, to remove fat cells and debris, which if left behind will necrose, potentially leading to wound infection. For all these reasons, irrigation with a hypochlorous acid containing irrigation solution in breast surgery prior to wound closure, may have benefits beyond standard practice (no wound wash or wound wash with sterile saline/water/povidone iodine).

Intervention 3: Dialkylcarbomoyl chloride (DACC)-coated dressings

Dressing use in breast surgery varies significantly in the UK from no dressing, to any one or combination of glue, steristrips, simple adhesive dressings, dressings impregnated with antibacterial substances and negative pressure wound therapy (NPWT). There is no high-quality robust data for any single type of dressing demonstrating improved wound outcomes in breast surgery, and surgeon choice remains the most common deciding factor. One RCT (n=230) suggested a lower SSI rate from using a silver-impregnated dressing compared to a standard wound dressing, but the difference was not statistical significant (6.6% vs 12.9%, RR 0.51, 95% CI 0.22-1.2, p=0.112) (31).

Dialkylcarbomoyl chloride (DACC)-coated dressings (Leukomed® Sorbact and Cutimed® Sorbact) irreversibly bind bacteria at the wound surface, thus removing the bacteria when the dressing is changed. A systematic review included 17 studies, with 4 (n=3,133 patients) of these considering clean surgical wounds (none in breast surgery) (32). The included RCT of 543 women undergoing caesarean section, demonstrated that the application of DACC dressings reduced the SSI rate to 1.8%, compared to 5.2% in the group receiving standard surgical dressings (p = 0.04), but was considered at risk of bias including poor treatment allocation and concealment methods, and lack of blinding of participants or investigators. Further high-quality research was therefore recommended into DACC dressing use to prevent SSI. A well designed RCT in vascular surgery randomising 720 patients to DACC dressings vs standard care (The DRESSINg trial Clinicaltrials.gov identifier: NCT02992951) (33) is currently recruiting.

NPWT dressings are of interest to reduce wound complications in breast surgery and there is some evidence that they reduce the risk of seroma, wound breakdown and implant loss in breast implant reconstruction (34-36), but other studies suggest no difference in complication rates (37), with larger studies called for to determine effectiveness. One recent small single centre RCT in high risk patients undergoing breast surgery (BMI over 29.9, diabetes mellitus, smoker, previous radiotherapy on the affected breast, and predisposing comorbidities such as collagen pathologies, vasculopathies, and previous neo-adjuvant chemotherapy of any kind) demonstrated a significant reduction in SSI in those treated with prophylactic NPWT dressings (38). The study however only included 100 patients and was considered at risk of bias so further large methodologically robust studies are needed.

NWPT will not be allowed as standard practice in this arm of the ROSSINI-Platform Breast pillar, as it is being investigated as an intervention in three other ROSSINI-Platform pillars (Vascular – major lower limb amputation, vascular – groin and cardiothoracic surgery). However, NWPT may be considered as an intervention for high-risk breast surgery patients as the ROSSINI-platform Trial evolves.

Given the promising evidence for DACC dressing in preventing SSI in clean wounds, demonstrating whether they have an effect in breast surgery is of interest when compared to standard practice (no dressing, glue dressing, steristrips dressing, non-coated occlusive dressing). NICE guidelines on DACC dressings currently recommend them as a cost-effective intervention in caesarean section and vascular surgery only, and further research in a range of surgical settings is welcomed (39).

3. PILLAR SPECIFIC PILOT AIMS AND OBJECTIVES

3.1 Internal pilot objectives

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

The pilot phase of the breast pillar will begin when the first patient is recruited to the pillar. The pilot phase will inform decisions on the continuation of the trial.

The aims of the internal pilot at Pillar level are to assess:

- Number of sites opened
- Number of patients recruited
- Engagement with the Centralised Digital Wound Hub(CDWH)
- Participant-level data at the Birmingham Clinical Trials Unit (BCTU)

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

Table 1: Breast PILLAR- Level Internal Pilot Progression Criteria

Progression Criteria	Number of sites opened	Participant recruitment	Engagement with CDWH*	Participant-level data to BCTU**
GREEN (GO)	≥ 10 sites	≥60 participants	≥95%	≥95%
AMBER (modify)	6 -9 sites	21 – 59 participants	≥ 90 - < 95%	≥ 90 - < 95%
RED (STOP)	≤ 5 sites	≤ 20 participants	< 90%	< 90%

* Percentage of participants submitting at least one response to CDWH

**Percentage of participants submitting baseline data to BCTU

Table 2: INTERVENTION-LEVEL Internal Pilot Progression Criteria

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

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

Intervention-level progression criteria relate to all interventions.

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

4. TRIAL DESIGN AND SETTING

4.1 Trial design

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

The target sample size for the BREAST pillar is 4,280 participants.

4.2 Trial setting

The BREAST Pillar will open in approximately 70 NHS trusts, representing about half of the approximate 130 breast surgery centres units in the UK (2). Sites will be selected based on ,ability and capacity to recruit, available resources to effectively recruit, geographical location and enthusiasm to take part. Recruiting sites will also be determined by the other pillars in ROSSINI-Platform who may be based in more specialist centres, but we intend to have broad participation from a wide range of UK breast surgery sites to maximise the external validity of the trial findings.

5. PILLAR-SPECIFIC ELIGIBILITY

5.1 Inclusion criteria

- Adult patients (18 and over) undergoing resectional surgery for breast cancer, including breast conservation surgery, mastectomy, oncoplastic surgery and axillary surgery.
- Patients able to provide informed consent

5.2 Exclusion criteria

- Patients undergoing breast surgery for breast cancer with whole breast reconstruction (i.e. implant reconstruction or autologous free flap reconstruction)
- Patients undergoing a re-excision of margins for cancer.
- For intervention 1: **Prophylactic antibiotics at induction**
    - Known allergy to any of the antibiotics used within the breast pillar
- For intervention 2: **Wound irrigation with Granudacyn® prior to closure**
    - Known allergy to any of the ingredients contained in Granudacyn®
- For intervention 3: **Dialkylcarbomoyl chloride (DACC)-coated dressings**
    - Known allergy to dialkylcarbomoyl chloride (DACC)-coated dressings

5.3 Co-enrolment

Patients with breast cancer may be eligible to participate in several oncology trials that are of national and international importance. It is anticipated that recruitment to the ROSSINI-Platform will not affect recruitment to most of these trials unless the intervention under investigation may impact the primary outcome of ROSSINI-Platform (SSI).

Co-enrolment in other perioperative trials (i.e. those involving interventions administered immediately before, during and immediately after surgery, before hospital discharge) will not be permitted for logistical and practical reasons.

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

6. PILLAR SPECIFIC CONSENT CONSIDERATIONS

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

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

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

7. RANDOMISATION and BLINDING

7.1 Randomisation method

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

Intervention 1 randomisation:

- Prophylactic antibiotics prior to commencement of surgery (intervention)
- No prophylactic antibiotics prior to commencement of surgery (control)

Intervention 2 randomisation:

- Wound irrigation with Granudacyn® prior to closure (intervention)
- Standard practice (no wound wash or wound wash with sterile saline/water/povidone iodine) (control)

Intervention 3 randomisation:

- Dialkylcarbomoyl chloride (DACC)-coated dressings (intervention)
- Standard practice (no dressing, glue dressing, steristrips dressing, non-coated occlusive dressing) (control)

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

- Centre
- BMI ($<30 kg/m^2$ OR $\geq 30 kg/m^2$)
- Smoking status (Current smoker or nicotine use [including vaping/use of nicotine with cannabis] OR previous smoker, OR never smoked)
- Diabetes (Yes (on medical therapy not including insulin) OR Yes (on insulin) OR Yes (diet controlled) OR No)
- Neo-adjuvant systemic therapy in prior 2 months (excluding endocrine therapy) (Yes OR No)

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

7.2 Blinding – BREAST Pillar-specific considerations measures

Measures will be taken to ensure blinding to the randomised allocation as described in the Master Protocol (Section 7.5).

Breast Pillar-Specific considerations are described below:

Intervention 1: Prophylactic antibiotics at induction

Intervention 2: Wound irrigation with Granudacyn® prior to closure

Intervention 3: Dialkylcarbomoyl chloride (DACC)-coated dressings

Both participants and in-hospital wound reviewers at discharge (outcome assessors) will be blinded to interventions 1 and 2.

It is not possible to blind participants or site research teams to intervention 3 due to the difference in appearance of dressings. Only the post-discharge wound review undertaken by CDWH will remain blinded to allocation in this arm.

8. PILLAR SPECIFIC TRIAL INTERVENTIONS

The standard of care for prevention of SSI in breast surgery is heterogenous across the UK. ROSSINI-Platform is a pragmatic RCT, but the minimum standard of care expected is to follow the NICE guidance NG125 on the prevention of SSI (19).

8.1 Standard care

As per NICE guidance NG125 (19), patients undergoing breast surgery will receive routine care to prevent SSI which will include (though not exclusively):

- Use of sterile drapes, gloves, gowns
- Alcohol based chlorhexidine skin preparation (or Alcohol-based solution of povidone-iodine if chlorhexidine contraindicated, or aqueous solution of povidone-iodine if both chlorhexidine and alcohol are contraindicated)
- Scalpel for skin incision (not diathermy)
- Monitoring and maintenance of patient normothermia, optimal oxygenation and tissue perfusion
- Consideration of use of anti-microbial triclosan coated sutures for skin closure (standard of care as per NICE (41) and ABS (42) guidance, and can therefore be used in all intervention and comparator arms of ROSSINI-Platform (Breast)).

8.2 Trial interventions

Intervention 1: ***Prophylactic antibiotics at induction***

A single dose of intravenous antibiotics should be administered at the induction of anaesthesia. Antibiotic choice at induction of anaesthesia will be as per breast unit policy, however type, dose and route will still be recorded. As *Staphylococcus aureus* is the commonest cause of breast SSI, most prophylactic antibiotic policies are likely to include flucloxacillin or co-amoxiclav, with teicoplanin, gentamycin or clindamycin being used if patients are penicillin allergic.

No additional doses of antibiotics either intravenously or orally should be given peri-operatively e.g. in recovery or on the ward post-operatively or to take home. If unit policy is to give antibiotics in combinations e.g. Flucloxacillin and Metronidazole, this ***is allowed*** in the trial. The antibiotic policy of each unit should be forwarded to the ROSSINI trial team as part of the site set up. The following table gives some example antibiotic regimes commonly used in breast surgery but ***is not an exhaustive list*** and any antibiotic or combination of antibiotics may be used in the trial if randomised to intervention 1.

Table 3: Intervention 1 - Example prophylactic antibiotic regimes prior to the commencement of surgery

Name of intervention	Comparator	Dose	Route of administration	Follow up
Flucloxacillin	No antibiotics	1g	Intravenous single dose at induction of anaesthesia	As per trial procedures
Co-amoxiclav	No antibiotics	625mg	IV single dose at induction of anaesthesia	As per trial procedures
Metronidazole	No antibiotics	500mg	IV single dose at induction of anaesthesia	As per trial procedures
Gentamycin	No antibiotics	1.5mg/kg	IV single dose at induction of anaesthesia	As per trial procedures
Teicoplanin	No antibiotics	400mg	IV single dose at induction of anaesthesia	As per trial procedures
Clindamycin	No antibiotics	400mg	IV single dose at induction of anaesthesia	As per trial procedures

Comparator 1: ***No antibiotics***

If randomised to the comparator arm, ***no antibiotics should be given peri-operatively,*** either in theatre, post operatively, or in the immediate post operative period (e.g. a prophylactic course of oral antibiotics on discharge).

If SSI is diagnosed in any patient in the trial, antibiotics may be given if medically indicated.

Intervention 2: *Wound irrigation with Granudacyn® prior to closure*

The wound and cavity should be irrigated with Granudacyn® prior to closure of the breast wound with surgeon choice of sutures. No other wound irrigation should be performed. There is no limit on the quantity of Granudacyn® that can be used to irrigate the wound, and this will vary depending on the size of the wound e.g. wide local excision vs mastectomy. Granudacyn® should be warmed to body temperature before use and poured into a sterile receptacle. Irrigation of the wound should be performed as per usual practice e.g. with a sterile jug, syringe or bulb syringe. Suction can be used depending on usual practice.

Comparator 2: ***Standard of care***

This may include wash with saline or povidone iodine or no wash

Prohibited comparator interventions:

- Irrigation with antibiotic solutions

Intervention 3: *Dialkylcarbomoyl chloride (DACC)-coated dressings*

The dressing should be applied at the end of the operation, once the wound has been closed with sutures, and the skin cleaned and dried. No other 'dressings' should be used (e.g. glue/use of steristrips). The dressing should remain in place for up to 7 days. If it becomes saturated and/or peels off, a further DACC dressing can be re-applied if needed.

Comparator 3: *Standard of care*

This may include no dressing, glue (any type/brand), steristrips and/or any other non-coated occlusive dressing.

Prohibited comparator interventions:

- Other ***coated*** occlusive dressings e.g. silver, honey, iodine impregnated dressings.
- **ALL** NPWT dressings including (but not exclusively) PICO 7 and 14 ™ (Smith&Nephew), Prevena ™ (Solventum), Invia Motion® (Medela), Renasys® (Smith&Nephew), VivanoTec® (Hartmann), VENTURI® Mino (Talley), Avelle ™ (ConvaTec)

8.3 Contraindications

Specific contraindications to each included intervention are:

Intervention 1:

- A known allergy to any of the antibiotics used in the breast pillar.

Intervention 2:

- A known allergy to any of the ingredients contained in Granudacyn®

Intervention 3:

- A known allergy to Dialkylcarbomoyl chloride (DACC)-coated dressings

8.3.1 Concomitant medication(s)/intervention(s)

Not applicable.

8.3.2 Prohibited medication(s)/intervention(s)

Not applicable.

8.4 Intervention modification or discontinuation

Intervention 1 (Prophylactic antibiotics prior to commencement of surgery) and **Intervention 2** (Wound irrigation with Granudacyn® prior to closure) are single use and only applicable intraoperatively.

Intervention 3 (Dialkylcarbomoyl chloride [DACC] -coated dressings) should be kept in place for up to 7 days. The dressings may need to be removed earlier if they become saturated, or the surrounding skin is inflamed or blistered indicating significant skin reaction or allergy. If the dressing is removed due to saturation or because it peels off before 7 days, a further DACC dressing can be applied up to a total of 7 days. All skin reactions should be photographically recorded and sent to the CDWH as part of the trial outcome follow up.

8.5 Cessation of treatment/ Continuation of intervention after the trial

Intervention 1 (Prophylactic antibiotics prior to commencement of surgery) and **Intervention 2** (Wound irrigation with Granudacyn® prior to closure) are single use and only applicable intraoperatively.

Intervention 3 (Dialkylcarbomoyl chloride [DACC] -coated dressings) should be kept in place for up to 7 days. As per section 8.4, if the dressing needs to be changed, it should be replaced with another DACC dressing, the DACC dressing should be removed at the end of 7 days. This can be done by the patient or carer and does not require a formal hospital visit or interaction with healthcare services.

8.6 Intervention supply and storage

8.6.1 Intervention supplies

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

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

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

Intervention 1: ***Prophylactic antibiotics at induction***

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

Intervention 2: ***Wound irrigation with Granudacyn® prior to closure***

- MOLNLYCYKE

Intervention 3: ***Dialkylcarbomoyl chloride (DACC)-coated dressings***

- ESSTIY

8.6.2 Packaging and labelling

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

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

8.6.3 Intervention storage

Those interventions being supplied free of charge, should be stored in a secure, clean, dry place free from damp at room temperature and within the supplied sterile packaging. No specific special requirements are required above the standard storage conditions of theatre products and refrigeration will not be necessary. Any excess intervention material will be disposed of in the hospital’s standard clinical waste bins as per local hospital protocol.

Interventions supplied for free must only be used for patients within the trial, randomised to the arm in question. Any centres using those interventions outside the trial setting may be cautioned, asked to withdraw from the trial or be asked for reimbursement.

8.6.4 Storage deviations

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

For any trial interventions that are from standard hospital stock, sites should follow local policies and SOPs.

8.6.5 Intervention recalls

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

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

8.6.7 Accountability

Each individual recruiting site shall be responsible for ensuring adequate stock of interventions required to adequately randomise participants to all arms in the pillar. Each site must ensure that stock levels are adequate prior to randomisation to avoid protocol deviation.

Intervention 1 is in routine use.

Intervention 2 will need to be delivered to central pharmacy and then stored in breast surgery theatres for use during the trial.

Intervention 3 will need to be delivered to breast surgery theatres.

9. PILLAR SPECIFIC ADVERSE EVENT REPORTING

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

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

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

- The reporting period for ALL safety events within the ROSSINI-Platform
- The process for reporting of ALL safety events within the ROSSINI-Platform
- SAEs common to all pillars requiring expedited reporting within the ROSSINI-Platform
- SAEs common to all pillars requiring non-expedited reporting within the ROSSINI-Platform

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

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

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

- Allergic reactions to any of the interventions

Events requiring expedited reporting should be reported on a SAE eCRF and provided to the ROSSINI-Platform Trial Office within 24 hours of site becoming aware of the event.

Events subject to expedited reporting and should be reported according to the process detailed in Section 11.5.3 of the Master Protocol.

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11. APPENDIX