ROSSINI-PLATFORM TRIAL

Pillar-Specific Protocol

OBSTETRIC

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

OBSTETRIC 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

All interventions used within the OBSTETRICS pillar are taken from standard hospital stock

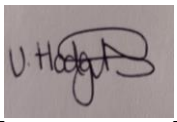
PROTOCOL SIGN OFF

Pillar Lead for Obstetrics -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 (OBSTETRIC Pillar)
Protocol version number:	Version:
Protocol version date:	__ __/__ __ __/__ __ __ __
Pillar Lead name:	Victoria Hodgetts Morton
Signature and date:	_____  _____ /2025

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 OBSTETRIC 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 OBSTETRIC 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, 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 (OBSTETRIC Pillar)
Protocol version number:	Version: __ __
Protocol version date:	__ __ /__ __ __ /__ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __ /__ __ __ /__ __ __ __

ADMINISTRATIVE INFORMATION

Trial office contact details	
Birmingham Clinical Trials Unit (BCTU) School of Health Sciences College of Medicine and Health Public Health Building University of Birmingham Birmingham B15 2TT	Tel: Email:
Randomisation website	< tbc >
Trial website	< tbc >
Trial social media	< tbc >

Pillar Trial Management Group	
Dr Vicky Hodgetts Morton	Pillar Lead Associate Professor and Honorary Consultant in Obstetrics University of Birmingham
Professor Katie Morris	Pillar Deputy Lead Professor of Obstetrics and Maternal Fetal Medicine
Dr Catherine Dunlop	Academic Clinical Lecturer in Obstetrics and Gynaecology University of Birmingham
Dr Sharon Morad	Consultant Obstetrician Birmingham Women's and Children's NHS Foundation Trust
Ms Lauren Yates	Research Midwife Birmingham Women's and Children's NHS Foundation Trust
Professor Thomas Pinkney	Chief Investigator George Drexler & Royal College of Surgeons Chair of Surgical Trials, University of Birmingham
Dr Laura Magill	Co-lead of Executive TMG Associate Professor in Clinical Trials, University of Birmingham
Mr Matthew Soden	Trial Management Team Leader, University of Birmingham
Ms Eleni Gkini	Medical Statistician, University of Birmingham
Dr Kelly Handley	Senior Medical Statistician, University of Birmingham
Mrs Amy Skinner	Programme Manager – ROSSINI-Platform, University of Birmingham
Ms Lisa Leighton	Senior Trial Manager, University of Birmingham

TBC	Patient and Public Representative

ABBREVIATIONS

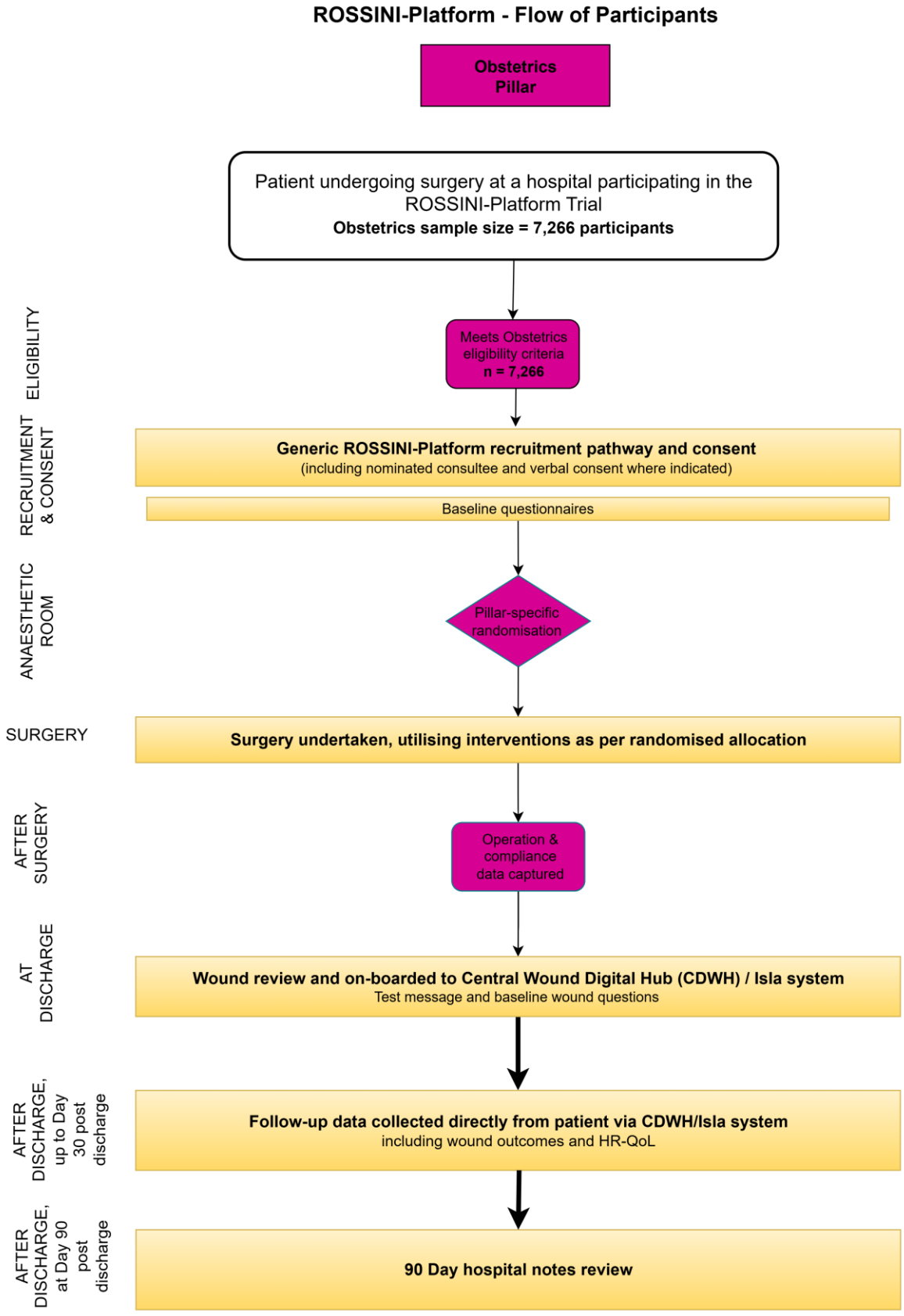
Abbreviation	Term
ANC	Antenatal Clinic
BCTU	Birmingham Clinical Trials Unit
CDWH	Centralised Digital Wound Hub
CI	Chief Investigator
CS	Caesarean Section
eCRF	Electronic Case Report Form
ETMG	Executive Trial Management Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
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
PI	Principal Investigator
PIS	Participant Information Sheet
PSP	Pillar Specific Protocol
RAG	Red, Amber, Green progression Criteria
REC	Research Ethics Committee
RSI	Reference Safety information
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Proceedure
SSI	Surgical Site Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
UK	United Kingdom
WHO	World Health Organization

ROSSINI PLATFORM: OBSTETRIC PILLAR TRIAL SUMMARY

INTERVENTIONS	• Vaginal cleansing prior to caesarean section • Additional prophylactic antibiotics after umbilical cord clamping • Instrument and glove change for closure at caesarean section (CS)
PARTICIPANT POPULATION AND SAMPLE SIZE	Women over 12 years of age giving birth via emergency or elective caesarean section. Sample size: 7,266 participants
PILLAR-SPECIFIC ELIGIBILITY CRITERIA **INCLUSIONS**	• Any patient undergoing emergency or elective CS • Patients aged 12 years and above • Patients, and/or parent/guardian for those under 16, willing to give informed consent. ~~• Vaginal cleansing:~~ ~~○ Gestational age must be greater than 34+0 weeks.~~ ~~*Gestational age is unrestricted for the additional antibiotic arm and the instrument and glove change arm.~~
PILLAR-SPECIFIC ELIGIBILITY CRITERIA **EXCLUSIONS**	• **Vaginal cleansing exclusions:** ○ Known allergy to chlorhexidine gluconate or any of its ingredients ○ Gestational age less than 34+0 weeks~~.~~ *Gestational age is unrestricted for the additional antibiotic arm and the instrument and glove change arm. • **Additional antibiotics exclusions:** ○ Known allergy to azithromycin or macrolide antibiotics ○ Already receiving azithromycin or another macrolide antibiotic for prophylaxis due to allergy ○ Patients with structural heart anomalies, cardiac arrythmias and taking any medication that prolongs the QT interval. ○ Known hypokalemia or hypocalcaemia ○ Known abnormal liver function • **Instrument and glove change:** ○ No intervention specific exclusions for this intervention arm
RECRUITMENT TARGETS	7,266 participants
TIMELINES	Up to 50 months of recruitment.

TRIAL SCHEMA



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1. PILLAR SPECIFIC PROTOCOL STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While, all adaptations are pre-specified, (e.g. the dropping or addition of interventions and/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 the ROSSINI-Platform Master Protocol (overview and design features of the study) and multiple Pillar-Specific Protocols (PSP) (detailing all interventions currently being studied in each Pillar).

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

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

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

2. BACKGROUND AND RATIONALE

2.1 Pillar definition

This is a Pillar within the ROSSINI-Platform Trial to test the effectiveness of specific peri-operative interventions to prevent Surgical Site Infection (SSI) in women undergoing a caesarean section (CS) within a UK National Health Service (NHS) maternity setting. This includes both emergency and elective caesarean sections. The following definitions are used within the protocol.

Table 1: Definitions

Elective caesarean section	This term relates to the timing of the caesarean section. All category 4 (at a time to suit the woman and maternity services) caesarean sections will be considered an elective caesarean section. This term will be used when describing recruitment and consent procedures.

Emergency caesarean section	This term relates to the timing of the caesarean section. All category 1 (immediate threat to life of woman or fetus), 2 (no immediate threat to life of woman or fetus) or 3 (requires early delivery) caesarean sections will be considered an emergency caesarean section. This term will be used when describing recruitment and consent procedures.
In labour caesarean section	This term relates to the risk factors for infections and thus in labour is considered as any woman with regular painful contractions and cervical change (dilatation or effacement), and/or ruptured membranes. This term will be used when specifying prognostic factors and in the collection of outcomes. This is a clinical interpretation of the clinician caring for the woman and we are asking for a clinical judgement of whether the woman is in labour/not in labour.
Not in labour caesarean section	The term relates to the risk factors for infection and thus not in labour is considered to be any woman who has no uterine activity, intact membranes and a closed cervix (all three factors must be present to be determined not in labour). This term will be used when specifying prognostic factors and in the collection of outcomes.

2.2 Pillar-specific background

Worldwide CS delivery is the most common major operation. Approximately 35 percent of pregnant women undergo a CS in the United Kingdom for delivery of their babies. This equates to at least 1000 caesarean sections at the average maternity site and approximately 171,000 CS per year in England alone.[1]

Sepsis and postnatal infection constitute significant maternal mortality and morbidity, varying from requirement for high dependency/ intensive care to milder infections that are managed in the community, but have significant impact on postnatal recovery and maternal wellbeing. Infection following a CS has a number of primary sources including with the uterus (endometritis) and within the deeper and superficial layers of the abdomen. Risk factors for infection following CS include in labour caesarean section, ruptured membranes with or without vaginal colonisation with group B streptococcus, emergency procedure and pre-existing maternal co-morbidity including diabetes and a raised BMI.[1]

Reducing infectious morbidity post-surgery has been identified as a national and international priority. Although there have been significant reductions in maternal mortality rates from sepsis, this is due to the introduction of sepsis care bundles and active treatment rather than reduction in rates of infection.

Impact of SSI

SSI after CS can lead to a prolonged hospital stay or readmission to hospital and an overall prolonged and more complex recovery process. In addition, an SSI after a CS impacts the mother-baby bonding, breastfeeding, separation, and psychological health.

Baseline SSI rates

SSI rates of 8-12% are typically reported in the literature. Yet in some high-risk groups infection rates are reported to exceed 20%. A conservative infection rate of 8.0% represents 16,150 women suffering from SSI after CS each year, of whom 980 may be expected to be readmitted (readmission rate is 6% in women with SSI after CS). Increased rates of infection are seen in women undergoing an emergency CS, those with ruptured membranes prior to CS, diabetes, long labour and multiple vaginal examinations.[2]

2.3 Pillar-specific rationale

2.3.1 Justification for pillar-specific participant population

Prophylactic antibiotics prior to the onset of surgery, have been demonstrated to be beneficial in a number of large randomised controlled trials (RCT) and continue to reduce infection rates.[3] Yet we must seek strategies to reduce this burden further. Being diligent to aseptic procedures in theatre is an important component of reducing infection rates. Current practice is for only skin preparation prior to incision at CS with a several RCTs demonstrating the superiority of a chlorhexidine over an iodine based solution for skin preparation. There are limited additional interventions applied to reduce SSI rates at CS and this forms rationale for this pillar, with the World Health Organization (WHO) detailing the importance of reducing the infectious mortality and morbidity of CS an important strategy in the fight against antimicrobial resistance. Three additional intraoperative interventions will be evaluated for effectiveness.

2.3.2 Justification for choice of interventions

Vaginal Cleansing

In addition to skin preparation with an antiseptic solution, cleansing inside the vagina with povidone iodine/chlorhexidine has been evaluated in a Cochrane review of 21 trials, reporting results for 7038 women evaluating the effects of vaginal cleansing (17 using povidone-iodine, 3 chlorhexidine, 1 benzalkonium chloride) on post-caesarean infectious morbidity. Vaginal preparation immediately before caesarean delivery significantly reduced the incidence of post caesarean endometritis from 7.1% in control groups to 3.1% in vaginal cleansing groups average risk ratio (aRR) 0.41, 95% confidence interval 0.29 to 0.58; 20 trials, 6918 women; moderate-certainty evidence. The risk reduction was particularly strong for women who were already in labour at the time of the caesarean delivery and for women with ruptured membranes. The above would appear an effective and important strategy to reduce morbidity at CS yet this has not been adopted within obstetric

practice internationally and does not feature within the National Institute for Health and Care Excellence (NICE) Intrapartum guideline. This is due to concerns with exposure of the fetus to iodine based substances, concerns with vaginal staining and allergy to iodine. Iodine is a recognized antibacterial agent, but local skin irritation and skin staining limits its use, which is overcome by the introduction of a stabilizing moiety, povidone. Povidone, which is water soluble, does not require a dissolvent such as alcohol and, thus, is less irritating to skin and mucosa surfaces. With povidone iodine, some women will still develop sensitivity and there are concerns including incorporation of iodine in body cavities unprotected by a keratinized epithelium, such as the vagina. In normal vaginal pH (3.8– 4.5), iodine's disinfecting properties are decreased and povidone iodine is inactivated by the presence of blood, invariably present in the vagina during a CS. Thus, there are a number of reasons to believe that vaginal cleansing with Chlorhexidine would be an appropriate alternative to povidone iodine. Chlorhexidine acts by causing destruction of bacterial cell membranes, leading to the leakage of cellular components and a decrease in bacterial counts. Some studies show greater reduction in skin flora after application of chlorhexidine (0.5% and 4%) compared with povidone-iodine agents. Also, chlorhexidine may have a greater residual activity after application than other preparations and, unlike povidone iodine; it is not inactivated by the presence of blood. To avoid irritation, chlorhexidine with high concentrations of alcohol (e.g, 70% isopropyl alcohol, commonly used for skin preparation) should not be used in the vagina. Solutions that contain lower concentrations, such as the commonly used aqueous chlorhexidine gluconate and acetate (0.05%) are usually well tolerated and may be used for vaginal preparation. With this preparation there are no reported cases of allergy. [4]

A Cochrane review of cleansing the vagina in normal vaginal delivery with chlorhexidine showed no evidence of an effect on maternal or neonatal infections with low to moderate confidence, although further large scale trials to detect small but clinically important differences were needed. Importantly no safety concerns for the mother or baby have been identified within these studies and it is reasonably to consider its use in a surgical procedure where rates of infection are higher.[4]

Addition of Azithromycin after cord clamping to prophylactic antibiotic regimen

Antibiotics given before skin incision at CS have been shown to reduce SSI, with international guidelines recommending a single dose of broad spectrum antibiotics prior to CS as routine practice.[3]

There is evidence that pre-operative azithromycin in addition to routine/standard antibiotics reduced wound infection and endometritis. A trial of Azithromycin given prior to skin incision identified a risk ratio of 0.51 (95% Confidence Interval 0.38-0.68). [5] However, it is not routine practice in the UK to utilise this antibiotic due to concerns around transplacental carriage to the fetus. Antibiotic prophylaxis is designed to reduce the bacterial load within the host to enable the body's natural immunological defences to function adequately. Historically, CS cephalosporin/ penicilin prophylaxis was recommended post-cord clamping due to neonatal concerns. However, in recent years there has been further evidence to refine this recommendation as it has been demonstrated that administering cephalosporins pre-incision, significantly reduces the risk of SSI

when compared to post-cord clamping with no neonatal adverse outcomes. This is thought to be due to the pharmacological properties of cephalosporin as it mainly targets skin flora and has a half-life of approximately 2 hours. Consequently, there is a narrow window of opportunity for effective antimicrobial prophylaxis and administrative timing is crucial to achieve adequate adipose tissue concentrations with this antibiotic. Azithromycin by comparison has very unique pharmacokinetics; firstly it is transported rapidly into the adipose tissue, the myometrium and is detectable within umbilical cord plasma and amniotic fluid within 20 mins. Secondly, unlike cephalosporin it protects against Ureaplasma which is thought to be a potential pathogen in wound infection and has also been associated with endometritis and postnatal infection blood cultures. Lastly, is has a 72-hour half-life thus administration prior to skin incision may not be as important in CS. Therefore, adjunctive azithromycin could be equally as beneficial given post-cord clamping as it is pre-incision which would eliminate the potential neonatal risks from transplacental passage. This is further supported by Andrews et al [6] Tita et al [5] and Tita et al [7] as all three studies saw a significant reduction in endometritis and wound infection even when azithromycin was administered post-cord clamping in secondary analysis of data. In light of this, further research is needed to determine its utility in women undergoing CS within the UK.

It is important to test whether a different timing of additional antibiotic - after cord clamping hence removing the risk of transfer to the neonate, could also be effective in reducing SSI. Qualitative research interviews by our group with women (n=15) highlighted that women are keen for interventions to reduce infection but also want to minimise risk to the baby from transplacental passage of antibiotics.

Surgical instrument and glove change after delivery of the baby and placenta

There is evidence that change of instruments and gloves at laparotomy closure reduces SSI. In trials evaluating this within caesarean sections the evidence is inconclusive. It is important that this intervention is assessed in CS at the stage of the operation when there is potentially the most risk of transfer of microorganisms i.e. after delivery of the placenta. A systematic review [8] highlighted the need for a large well conducted trial ensuring attention was paid to the timing of the intervention and ensure all members conformed to this change. When performed after delivery of the placenta the review suggested a reduction in SSI but highlighted the need for a full effectiveness evaluation.

3. PILLAR SPECIFIC 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 obstetrics 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, with a representative split across emergency and elective caesarean sections
- Engagement with the Centralised Digital Wound Hub (CDWH)
- Participant-level data at the Birmingham Clinical Trials Unit (BCTU).

Table 2: PILLAR Level Internal Pilot Progression Criteria

Progression Criteria	Number of sites opened	Participant recruitment	Engagement with CDWH*	Participant-level data to BCTU**
GREEN (GO)	≥ 12 sites	≥ 80 participants	≥ 95%	≥ 95%
AMBER (modify)	7 - 11 sites	31-79 participants	≥ 90 - < 95%	≥ 90 - < 95%
RED (STOP)	≤ 6 sites	≤ 30 participants	< 90%	< 90%

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

Table 3: 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.

3.2 Main trial - Pillar specific secondary objectives

Within the Obstetric Pillar there is one pillar-specific secondary objective:

Secondary Objective:

Do the peri-operative interventions:

- Reduce the rates of endometritis up to 30-days post delivery?
- Impact on antibiotic treatment for obstetric SSI?

4. TRIAL DESIGN AND SETTING

4.1 Trial design

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

The target sample size for the OBSTETRIC pillar is 7,266 participants.

4.2 Trial setting

The OBSTETRIC Pillar will open in approximately 20 NHS trusts in the UK.

The lead site for the trial is Birmingham Women's Hospital, a specialist women's hospital where over 2500 caesarean sections are performed each year. Outside the lead site the trial sites that can open multiple arms of the ROSSINI-Platform trial will be prioritised. Sites must run at least 2 of the intervention arms, only if an intervention arm is already established within a given site can a site choose not to participate in that randomisation.

5. PILLAR-SPECIFIC ELIGIBILITY

5.1 Inclusion criteria

- Any patient undergoing emergency or elective CS
- Patients aged 12 years and above
- Patients, and/or parent/guardian for those under 16, willing to give informed consent.
- ~~For vaginal cleansing gestational age must be greater than 34+0 weeks.~~

~~Gestational age is unrestricted for the additional antibiotic arm and the instrument and glove change arm.~~

5.2 Exclusion criteria

- **Vaginal cleansing exclusions**
  - Known allergy to chlorhexidine gluconate or any of its ingredients

- Gestational age less than 34+0 weeks

- **Additional antibiotics exclusions**
  - Known allergy to azithromycin or macrolide antibiotics
  - Already receiving azithromycin or another macrolide antibiotic for prophylaxis due to allergy
  - Structural heart anomalies, cardiac arrythmias and taking any medication that prolongs the QT interval
  - Known hypokalemia or hypocalcaemia
  - Known abnormal liver function

- **Instrument and glove change**
  - There are no intervention specific exclusions for this intervention arm

*Gestational age is unrestricted for the additional antibiotic arm and the instrument and glove change arm.

5.3 Co-enrolment

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

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

6. PILLAR SPECIFIC CONSENT CONSIDERATIONS

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

The processes for informed consent are detailed within the Master Protocol, and the options for provision of informed consent are described and must be followed for this pillar.

There are however, specific consent considerations for the obstetric pillar: :

- Verbal consent can be used for emergency caesarean sections
  Pathways for recruitment, consent and randomisation differ for emergency and elective CS due to differences in planning for surgery.

All women booking at any of the participating hospitals during the trial recruitment- period and who are pregnant should be sent/given a patient information sheet (PIS). Dissemination of PISs will be via email, antenatal (ANC) appointments and on admission to hospital. This will ensure that all potential participants are aware of the study prior to birth of their baby/babies. Trial posters will also be displayed in prominent positions through the hospitals.

Elective caesarean sections:

Women undergoing elective CS will be approached and invited to take part in the study, at either the time of booking of an elective CS in the antenatal clinic, during the preoperative visit or on the labour ward on the day of surgery. A suitably qualified research midwife or doctor will introduce the study to the woman, a PIS will be given and then time to consider the study will be given. Women will be given adequate opportunity to ask questions and consider their participation in the trial prior to written consent being obtained. Eligibility for the trial must be confirmed by a medically qualified member of the site research team.

Emergency caesarean sections:

It is appreciated that time can be limited in the undertaking of an emergency CS, especially where there is suspected maternal or fetal compromise. In keeping with the Royal College of Obstetricians and Gynaecologist consent advice for women participating in research, as long as information is available antenatally it is reasonable to take consent in labour. Therefore, all women booking at sites will receive information regarding the trial in the antenatal period and if appropriate in the intrapartum period such as during an induction of labour. The common incidence of CS (an event that occurs in 30% of birthing women) and the expectation of women in labour that CS is a possibility means that giving information to all women would not overburden them and is unlikely to cause anxiety or deviate women from the normal birth process.

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 CS procedure and before discharge.

In an emergency, where verbal consent is being taken, a suitably qualified research midwife/nurse or doctor will discuss the study with the women. A verbal discussion will include confirmation that the woman has previously received information regarding the trial, understands that the choice of intervention will be made randomly and is happy to take part. Eligibility for the trial must be confirmed by a medically qualified member of the site research team.

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 she is free to refuse to take part and may withdraw from the trial at any time. If she is happy to continue to participate in the trial, she will be asked to sign and date the latest version of the Informed Consent Form (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. The approach following delivery will be sensitive to the mother and babies needs and will not impact on care and time to bond as a family.

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:

- ***Vaginal Cleansing*** (Intervention)
- ***Standard practice of no cleansing*** (Control)

Intervention 2 randomisation:

- ***Addition of Azithromycin after cord clamping to prophylactic antibiotic regimen*** *(Intervention)*
- ***Standard prophylactic antibiotic regimen*** (Control)

Intervention 3 randomisation:

- ***Surgical instrument and glove change after delivery of the baby and placenta*** (Intervention)
- ***Standard practice*** (Control)

After the woman's eligibility has been confirmed by a medically qualified member of the site research team and informed consent has been received, the woman can be randomised into the trial.

Randomisation can be performed by all members of the research team and clinical team, and is most likely to be performed by dedicated research midwives.

Randomisation will be provided by a secure database randomisation where each user has a personalised logon or a secure telephone randomisation system available 8am to 6pm Monday to Friday. The telephone randomisation service will comply with research and governance standards.

The telephone randomisation service will be available by dialling the randomisation telephone number at the front of the protocol.

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

- Centre
- Elective (cat 4 and 3 CS) vs Non elective CS (cat1 or 2)
- Ruptured membranes at the time of CS vs non-ruptured membranes

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 – Obstetric pillar-specific considerations

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

Obstetric Pillar-Specific considerations are described below:

The trial cannot be blinded to the operator or the clinical care team in theatre providing care to the women due to the nature of the interventions. Randomisation will be performed by a wide range of staff from theatre runners to consultants. Randomisation may also be performed by dedicated research midwives who will also collect baseline data from the notes, but the outcome collectors will remain blinded to the allocations.

Attempts will be made to blind the women as the intervention will be applied at varying time point intraoperatively and they should not be aware of the whether they have been allocated to interventions or standard practice.

Blinding considerations

Vaginal cleansing:

This is a single-blind arm, women will be blinded to the allocation, the intervention will be provided at the time of catheter insertion under anaesthesia.

Additional antibiotics:

This is a single-blind arm, women will be blinded to this allocation, in most cases we anticipate the research team will also not be aware of the allocation as the intervention will be delivered by the anaesthetist and prescribed on the drug chart as per the routine prophylaxis antibiotics. The cost of azithromycin/placebo solution made up in advance in pharmacy would be prohibitive both financially and in limiting the ability of teams to recruit emergency patients outside of pharmacy hours.

Instrument and glove change:

This is a single blinded arm, women will be blinded to the allocation, in most cases we anticipate the research team will also not be aware of the allocation as the intervention will be performed by the surgical team during the operation after delivery of the placenta.

General considerations

Having discussed with co-applicants and BCTU we do not feel that a single blinded design of each arm will impact the validity of our results as the outcomes are objective and this is a common trial design in SSI trials. The single blinded design will improve acceptability to clinicans (related to risk of adverse drug/skin reactions).

8. PILLAR SPECIFIC TRIAL INTERVENTIONS

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

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

- The monitoring and maintenance of normothermia
- Use of a standard three-stage WHO Surgical Safety Checklist

8.1 Standard care

This is designed to be a pragmatic trial and therefore we have a limited set of standard operating procedures.

Prophylactic antibiotics as recommended by WHO should be given as soon as possible in theatre and ideally 15 minutes before skin incision and before the trial antibiotics.

Skin preparation, surgical technique and dressings are at the discretion of the surgical team.

8.2 Trial interventions

Intervention 1: Vaginal Cleansing

Chlorohexidine gluconate 0.05% (Unisept) or Chlorohexidine acetate 0.05% will be used to perform vaginal cleansing. This is indicated within the British National Formulary for swabbing in obstetrics.

Fifty mls of antiseptic (Unisept or Chorohexidine acetate 0.05%) to be emptied into a sterile pot. A single swab/sponge mounted on a sponge holder soaked in the antiseptic will be used to clean the vagina prior to CS at the time of urinary catheter insertion, for guidance we suggest the vaginal cleansing should take 30 seconds. Following the CS procedure the vagina will be cleaned of excess blood as is standard practice with a dry swab.

The application of the intervention is quick and familiar to the doctors performing the surgery due to their experience in gynaecological surgery where it is routine practice. We have evaluated providing additional equipment but feel the most efficient way of doing this is to follow the established method used in major gynaecological surgery where one swab on a stick is placed on the catheter trolley with a galley pot of chlorhexidine for the surgeon to cleanse the vagina at the time of routine catheter insertion.

All theatres' standard operating procedures regarding swabs and instrument counts should be adhered to, to ensure patient safety.

Comparator 1: No vaginal cleansing

No vaginal cleansing.

Intervention 2: Change of instruments and gloves immediately before uterine closure after delivery of placenta

This intervention describes an intra-operative procedural change whereby all scrubbed surgical team members change their gloves after delivery of the placenta immediately before closure, and they utilise a set of sterile new/untouched instruments from this point onwards.

- Clean instruments should be set to one side if using instruments from the main tray (e.g. needle holder, forceps, suture scissor tied/covered in a swab).

- **Gloves**: Change of sterile gloves (or outer gloves if double gloved) for all scrubbed members of the operating team including the surgeon, all assistant surgeon(s) and scrub staff.

- **Instruments**: A sterile set of instruments for uterine and abdominal closure including a needle holder, forceps, scissors and retractor. This should be implemented in each hospital according to local practice and availability. For example, they can be separated from the main instruments at the start of the operation by the scrub nurse (e.g. wrapped in a clean swab).
  During the procedure needle holders must not be stored in the side pockets of the drapes as these will have been contaminated with blood and liquor.

Comparator 2: In the control arm, current routine hospital practice without mandating changing gloves or instruments at anytime during the procedure should occur. On occasion, changing gloves or instruments will occur at other points during the operation according to any concerns regarding safety.

Intervention 3: Additional prophylactic antibiotics (Azithromycin)

A single dose of azithromycin (500mg IV) administered as soon as possible after cord-clamping and prior to skin closure and in addition to routine antibiotic prophylaxis which will be given prior to the start of the procedure.

Comparator 3: none.

8.3 Contraindications

Specific contraindications to each included intervention are:

Intervention 1: Vaginal Cleansing

- The intervention is licensed for use in obstetrics over 34 weeks for swabbing as per the Summary of Product Characteristics (SmPC), therefore it is contraindicated prior to 34 weeks.

- Allergy to Chlorohexidine gluconate 0.05% (Unisept) or Chlorohexidine acetate 0.05% or any of its ingredients.

Intervention 2: Surgical instrument and glove change

No contraindications.

Intervention 3: Additional prophylactic antibiotics (Azithromycin)

- Known allergy to azithromycin, erythromycin or any of the macrolide antibiotics.
- Already receiving azithromycin or another macrolide antibiotic for prophylaxis due to allergy
- Structural heart anomalies, cardiac arrythmias and taking any medication that prolongs the QT interval.
- Known hypokalemia or hypocalcaemia
- Known abnormal liver function

8.3.1 Concomitant medication(s)/intervention(s)

Azithromycin should not be co-administered with ergot derivatives because of the theoretical possibility of ergotism.

8.3.2 Prohibited medication(s)/intervention(s)

There are no prohibited medications or interventions.

8.4 Intervention modification or discontinuation

Given that all interventions are used peri-operatively or administered only once, there are no intervention modification considerations.

8.5 Cessation of treatment/ Continuation of intervention after the trial

All interventions are used only once during a participant's involvement in the trial. There is no requirement for continuation after the trial.

8.6 Intervention supply and storage

8.6.1 Intervention supplies

Within the Obstetric Pillar all interventions used are from standard hospital stock.

Intervention 1: Vaginal Cleansing with aqueous chlorhexidine

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

Intervention 2: *Change of instruments and gloves prior to closure*

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

Intervention 3: Azothromycin after cord clamping (500mg iv single dose)

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

8.6.2 Packaging and labelling

As all intervention used within the Obstetrics Pillar are from standard hospital stock and are administered or used within the operating theatre, there are no trial-specific packaging or labelling requirements.

8.6.3 Intervention storage

The theatre teams will store products (Aqueous chlorhexidine and Azothromycin) in accordance with product data sheets and as per local Policies and Standard Operating Procedures (SOPs).

8.6.4 Storage deviations

Any storage deviations will be handled in line with the sites local policies and SOPs.

8.6.5 Investigational Medicinal Product recalls

In the event that a trial product is recalled by the manufacturer, sites should follow usual Trust procedures / recall SOPS for any intervention recalls.

8.6.6 Accountability

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

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

9. PILLAR SPECIFIC SECONDARY OUTCOME MEASURES

Within the Obstetric Pillar there are two pillar-specific secondary outcomes:

- Endometritis within 30 days of delivery, with Day 0 as day of delivery.

  Endometritis is defined according to the CDC definition as the presence of at least two of the following signs with no other recognised cause:

  - fever (temperature of at least 38°C [100.4°F])

  - abdominal pain
  - uterine tenderness
  - purulent drainage from the uterus.

- Antibiotic treatment for obstetric SSI, with Day 0 as day of delivery
  - Antibiotics prescribed (day 0-42) for suspected/confirmed SSI relating to the woman's CS (uterine, pelvic, abdominal wound, or perineal).

10. PILLAR SPECIFIC ADVERSE EVENT REPORTING

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

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

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

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

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

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

There are no obstetric pillar specific expedited SAEs and no neonatal SAEs. The rationale for this is detailed below.

Azithromycin is FDA pregnancy category B – animal studies using maternally toxic doses showed no fetal harm. However, there are "no adequate well-controlled studies in pregnant women. It is not known whether azithromycin is excreted in human milk". The only absolute contraindication is known hypersensitivity reaction to azithromycin, erythromycin or other macrolide antibiotic (quite rare). There are no specific drug-drug interactions warranting dose adjustments when given with other medications. Elimination is by both renal and hepatic route, and no specific adjustments are mandated for patients with renal or hepatic insufficiency. The long elimination 1/2-life of 68 hours is due to extensive uptake and subsequent release of drugs from tissues. With multi-dose intravenous therapy, 1.2% of patients discontinued azithromycin due to clinical or laboratory effects. Potential adverse events include very rare (<<1%) allergic hypersensitivity (mild and severe

skin reactions – Stevens Johnson Syndrome and toxic epidermal necrolysis, angioedema and anaphylaxis), clostridium difficile-associated diarrhea and local intravenous site reactions. The azithromycin infusion should be stopped if there is evidence of evolving hypersensitivity such as new onset generalized rash and angioedema. Because local site reactions (7%) occur at higher concentrations, azithromycin is given at concentrations of 2mg/ml (i.e. 500mg in 250cc) or less. Gastrointestinal symptoms (diarrhea 4-8%, abdominal pain 2-3%, nausea 4-6% and vomiting 1-3%) are the most commonly reported side effects.

Pregnancy

There are no adequate data from the use of azithromycin in pregnant women. Azithromycin should only be used during pregnancy if definitely indicated. In this trial azithromycin is being administered after clamping of the cord and thus there will be no exposure to the fetus/baby. Thus, there will be no reporting of congenital anomalies.

Breastfeeding

Azithromycin passes into breast milk. Due to the low levels of azithromycin in breastmilk and the use of azithromycin in higher dosing levels in neonates it would not be expected to cause any problems.

In this trial a single dose of intravenous azithromycin is being given immediately after birth. Peak plasma concentrations are attained 2-3 hours after taking the medicinal product with trough levels at 24 hours.

Neonatal Pyloric Stenosis: Postnatal exposure to erythromycin has been associated with up to a 7-fold increase in pyloric stenosis particularly with exposure during the first two weeks (up to 10-fold increased risk)[56-57]. However, large studies of prenatal erythromycin exposure have not found an increased risk, although non-erythromycin macrolides have been associated with a small unexpected increase in pyloric stenosis attributed to chance [57-59]. No specific association with prenatal or postnatal azithromycin has been reported. As azithromycin is being given post cord clamping in this study and there is minimal exposure from breast milk, there will be no monitoring for neonatal outcomes.

9.2 Reference Safety Information Document

The Reference Safety Information (RSI) for the Obstetric pillar within the ROSSINI-Platform trial is Section 4.8 Undesirable Effects of the SmPC for azithromycin (Zedbac 500mg powder for solution for infusion from Aspire Pharma Ltd)

This should be referred to for all safety events experienced by participants within the Obstetric pillar as appropriate.

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11. APPENDIX