# ROSSINI-PLATFORM TRIAL

# Pillar-Specific Protocol

# NEUROSURGERY

## 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**

# NEUROSURGERY 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

The interventions used within the Neurosurgery pillar are all taken from standard hospital stock.

# PROTOCOL SIGN OFF

## Pillar Lead for Neurosurgery - 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 (NEUROSURGERY Pillar) |
| **Protocol version number:** | Version: __ __ |
| **Protocol version date:** | __ __/__ __ __/__ __ __ __ |
| | |
| **Pillar Lead name:** | Ms Ellie Edlmann |
| **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 NEUROSURGERY 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 Neurosurgery 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 (NEUROSURGERY 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)<br>School of Health Sciences<br>College of Medicine and Health<br>Public Health Building<br>University of Birmingham<br>Birmingham<br>B15 2TT | Tel:<br>Email: |
| Randomisation website | < tbc > |
| Trial website | < tbc > |
| Trial social media | < tbc > |

| Pillar Trial Management Group | |
|---|---|
| Ms Ellie Edlmann | Pillar Lead<br>Associate Professor of Neurosurgery, University of Plymouth |
| Professor Michael Jenkinson | Pillar Deputy Lead<br>Sir John Fisher Foundation / RCSEng Chair of Surgical Trials and Professor of Neurosurgery, University of Liverpool |
| *PPI lead TBC* | Patient and Public Involvement Representative |
| Mr Eric Ganitano | Band 7 neurosurgery lead research nurse specialist<br>University hospitals Plymouth NHS Trust |
| Professor Thomas Pinkney | Chief Investigator for the ROSSINI-Platform Trial<br>George Drexler & Royal College of Surgeons Chair of Surgical Trials, University of Birmingham |
| Dr Laura Magill | Co-lead of Executive TMG<br>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<br>University of Birmingham |

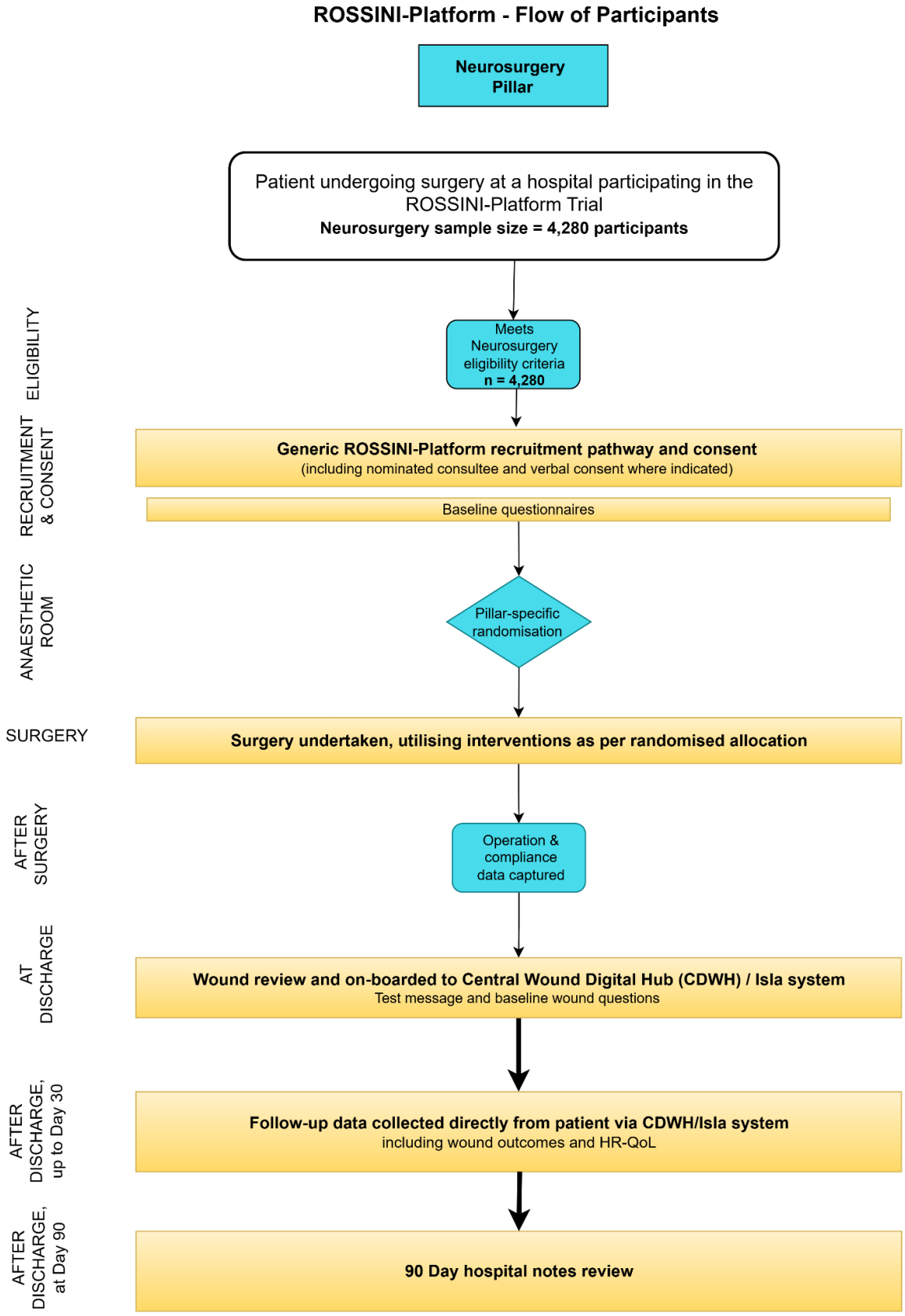
# ABBREVIATIONS

| | |
|---|---|
| ARR | Absolute Risk Reduction |
| BCTU | Birmingham Clinical Trials Unit |
| CDWH | Centralised Digital Wound Hub |
| CI | Chief Investigator |
| eCRF | Electronic Case Report Form |
| ETMG | Executive Trial Management Group |
| GCP | Good Clinical Practice |
| GIRFT | Getting it Right First Time |
| HRA | Health Research Authority |
| MAMS | Multi Arm Multi Stage |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| PI | Principal Investigator |
| PSP | Pillar Specific Protocol |
| REC | Research Ethics Committee |
| RSI | Reference Safety Information |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SCP | Surgical Care Practitioner |
| SOP | Standard Operating Proceedure |
| SSI | Surgical Site Infection |
| TSC | Trial Steering Committee |
| UK | United Kingdom |
| WHO | World Health Organization |

# ROSSINI PLATFORM: NEUROSURGERY PILLAR TRIAL SUMMARY

| | |
|---|---|
| **INTERVENTIONS** | 1. Bone flap stored in betadine (versus stored in saline)<br>2. Large volume (>1L) wound irrigation prior to closure (versus standard practice).<br>3. Topical Vancomycin powder under scalp flap (versus none). |
| **PARTICIPANT POPULATION AND SAMPLE SIZE** | **Participant Population** = approx. 11,000 craniotomies each year in the UK.<br>• If 80% patients are eligible across 80% of sites = 7,040/year.<br>• Recruitment rate of 30% = 8,800 recruitable patients over 50 months.<br>**Sample size calculation;**<br>• 5% baseline SSI rate, with 2% ARR = sample size 4,280 |
| **PILLAR-SPECIFIC ELIGIBILITY CRITERIA**<br>**INCLUSIONS** | **Inclusion criteria;**<br>• Patients aged ≥12 years, undergoing a craniotomy for any reason |
| **PILLAR-SPECIFIC ELIGIBILITY CRITERIA**<br>**EXCLUSIONS** | **Exclusion criteria;**<br>• Decompressive craniectomy (where there is no plan to replace the whole bone flap)<br>• Presence of or planned insertion of, an intracranial implant or device (e.g. external ventricular drain, ventriculoperitoneal shunt)<br>• Known or suspected intracranial infection<br>• For Intervention 1: Bone flap stored in betadine<br>  ○ Allergy or known hypersensitivity to aqueous betadine<br>• For intervention 3: Topical Vancomycin powder<br>  ○ Patients weighing less than 25kg<br>  ○ Known allergy or contra-indication to vancomycin<br>  ○ Patients with previous or current hearing loss are contra-indicated to vancomycin |
| **RECRUITMENT TARGETS** | Recruitment target is 4,280 participants over 50 months across 23 sites.<br>• Approximately 86 patients/month<br>• Recruitment rate 3-4 patients/month/site |
| **TIMELINES** | 50 months of recruitment |

## TRIAL SCHEMA



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# 1. PILLAR SPECIFIC PROTOCOL STRUCTURE

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

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

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

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

Each substantial modification to a PSP will require regulatory approval.

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

# 2. BACKGROUND AND RATIONALE

## 2.1 Pillar definition

This is a Pillar within the ROSSINI-Platform Trial to test the effectiveness of specific peri-operative interventions to prevent Surgical Site Infection (SSI) in patients undergoing a craniotomy.

## 2.2 Pillar-specific background

Cranial SSI can lead to bone flap infection, surgical meningitis, ventriculitis, empyema and brain abscess which are often life threatening and can cause major neurological disability. Cranial SSI is treated aggressively with bone flap removal and wound debridement, and prolonged admission for intravenous antibiotics. Patients need further surgery to reconstruct the skull with a substitute bone flap (cranioplasty), which itself carries major risks of neurological disability and death. The patient impact and NHS costs of cranial SSIs are substantial. In a local survey on 100 patients, where 11 had

suffered an SSI, of those 100 patients surveryed 95% identified SSIs as “extremely important” and 91% would participate in a trial.

**Baseline SSI rates**

Large prospective cohort studies report SSI rates in cranial neurosurgery of 2.5% - 15.3%[1]. The mean SSI rate of deep infection from audit data from our UK neurosurgery SSI working group was 5% (range 1-6%). The 2019 UK Getting it Right First Time (GIRFT) National survey on SSI reported a rate of 5.0-8.5% in cranial tumour operations (*GIRFT report)*[2].

## 2.3 Pillar-specific rationale

### 2.3.1 Justification for pillar-specific participant population

The participant population will include any patient who is under-going a craniotomy for any reason. The indications for craniotomy are wide, but most commonly include cranial tumour (benign or malignant), traumatic brain injury and vascular abnormalities. Despite the wide-ranging underlying pathology, the surgical techniques around access to the brain via a window in the skull (craniotomy) are relatively standard and it is this opening of the skull which predisposes to infection within or around the brain. There is no evidence to suggest that one neurosurgical patient group is any more likely than another to experience SSI[3] and to be as pragmatic and broadly applicable as possible, this trial will be inclusive of all pathologies. The exceptions are where implants are used, for example, temporary external ventricular drain, as clearly this increases the risk of infection due to foreign material being implanted, and where the bone flap is not replaced as this potentially alters the wound closure.

### 2.3.2 Justification for choice of interventions

**Intervention1: Bone flap stored in betadine (versus stored in saline)**:

During the initial surgical opening, the bone flap is removed from the head to allow access to the cranial contents. This must then be stored for the duration of the operation (which can be several hours) before replacement. Current practice amongst the hospitals in our working group varied between placing the bone flap in saline or an anti-septic solution (betadine). There is no evidence base for either practice but it is reported in neurosurgical training manuals and therefore managed as per the surgeons’ preference[4]. Randomisation between these options is cheap, easy and acceptable to almost all surgeons.

**Intervention 2: Large volume wound irrigation prior to closure (versus standard practice).**

Warm irrigation is used throughout cranial neurosurgery to maintain tissue moisture and warmth, remove bone dust and fragments and aid haemostasis. The volume of irrigation used varies greatly and our group felt that increased volumes of irrigation are likely to contribute to a lower infection rate, both by diluting potential pathogens and maintaining tissue moisture and thus integrity. This

intervention would randomise between a dedicated large volume warm saline wash at the end of surgery once the dura is closed and bone flap replaced compared to surgeons' standard practice. Standard practice ranges from no wash to small/unmeasured wash at time of closure. Saline irrigation has been shown to reduce shunt infections in a retrospective cohort study (13% to 1%), with no benefit to the addition of antibiotics[5].

**Intervention 3: Topical Vancomycin powder (versus none).**

Several small studies from America and Korea have reported the use of topical vancomycin powder in the subgaleal space to reduce SSI in craniotomies and a recent meta-analysis supported its use in reducing infections (Odds Ratio 0.13), but identified a lack of high-quality data and the need for randomised trials[6]. A 2025 meta-analysis on 2510 craniotomy patients reported significantly lower wound infections with topical vancomycin (1.2%) compared to controls (5.36%)[7]. Most studies in this meta-analysis used 1g of topical vancomycin powder (range 0.5-2g), across adult and paediatric patients. High quality randomised controlled trial data is still outstanding and therefore there is justification to assess topical vancomycin in this trial setting.

# 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 neurosurgery 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 3-month internal pilot phase, the Executive Trial Management Group (ETMG) and Trial Steering Committee (TSC) will review the pilot data against a set of pre-specified Red-Amber-Green (RAG) criteria:

**Table 1: PILLAR Level Internal Pilot Progression Criteria**

| Progression Criteria | Number of sites opened | Participant recruitment | Engagement rate with CDWH* | Participant-level data to BCTU** |
|---|---|---|---|---|
| GREEN (GO) | ≥ 6 sites | ≥40 participants | ≥95% | ≥ 95% |

| | | | | |
|---|---|---|---|---|
| AMBER (modify) | 3 - 5 sites | 11-39 participants | ≥ 90 - < 95% | ≥ 90 - < 95% |
| RED (STOP) | ≤ 2 sites | ≤ 10 participants | < 90% | < 90% |

* Percentage of participants submitting at least one response to CDWH

**Percentage of participants submitting baseline data to BCTU

**Table 2: INTERVENTION-LEVEL Internal Pilot Progression Criteria**

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

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

**Intervention-level progression criteria relate to all interventions.**

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

# 4. TRIAL DESIGN AND SETTING

## 4.1 Trial design

The Neurosurgery 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 Neurosurgery Pillar represents one of the phase III factorial MAMS RCTs.

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

## 4.2 Trial setting

There are 29 neurosurgical centres in the UK and a further 7 paediatric-only neurosurgical units. The Neurosurgery Pillar will aim to open in approximately 23 NHS trusts in the UK including 5 centres providing joint or paediatric-only care.

# 5. PILLAR-SPECIFIC ELIGIBILITY

## 5.1 Inclusion criteria

Patients aged ≥12 years, undergoing a craniotomy.

## 5.2 Exclusion criteria

- Decompressive craniectomy where there is no plan to replace the whole bone flap.
- Presence of, or planned insertion of, an intracranial implane or device (e.g. external ventricular drain, ventriculoperitoneal shunt)
- Known or suspected intracranial infection
- For Intervention 1: Bone flap stored in betadine
    - Allergy or known hypersensitivity to aqueous betadine
- For intervention 3: Topical Vancomycin powder
    - Patients weighing less than 25kg
    - Known allergy or contra-indication to vancomycin
    - Patients with previous or current hearing loss are contra-indicated to vancomycin

## 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. This includes the MAST (Management of Seizures after Traumatic Brain Injury) trial, STOP-EM (Surgeons Trial Of Prophylaxis for Epilepsy in seizure naive patients with Meningioma), TOP-TBI (Timing of venous thromboembolism prophylaxis for adult patients with traumatic brain injury), SCARF-BT (Social Cognition Assessment and Rehabilitation for Families living with Brain Tumour) and RESTART-tICrH (Restart Traumatic Intracranial Hemorrhage).

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

# 6. PILLAR SPECIFIC CONSENT CONSIDERATIONS

The process for informed consent is detailed within the Master protocol. The options for provision of informed consent are described therein and must be followed.

Within the Neurosurgery Pillar target population there are specific considerations for the provision of informed consent. This pillar will include three forms of informed consent:

1. Patients able to provide informed consent
2. Personal consultee/ legal representative for patients unable to consent themselves
3. Personal consultee consent/assent for children

Many patients with neurosurgical conditions may lack capacity or even be in a coma prior to surgery. In such cases, a representative will be sought to establish the patient's wishes and consent on their behalf if appropriate. This can be written, electronic or remote consent, as many patients will be transferred to their regional neurosurgical centre for treatment which may be far away from their home and local hospital, and a patient representative may not be available on site. Where possible, documented electronic consent will be collected, but witnessed telephone consent can also be used in case the representative does not have access to electronic documents or there is insufficient time in the case of emergency neurosurgery.

In some settings (e.g., cranial trauma), surgery will be performed as an emergency within hours of admission, and the patient may be in a coma with no personal consultee immediately available. In this setting it may be appropriate to recruit the patient using an Independent Healthcare Professional (IHP) consent.

# 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:

- ***Bone flap stored in betadine*** (intervention)
- ***Bone flap stored in saline*** (control)

Intervention 2 randomisation:

- ***Large volume wound irrigation prior to closure*** (intervention)
- ***Surgeons' standard practice*** (control)

Intervention 3 randomisation:

- ***Topical Vancomycin powder (500mg)*** (intervention)
- ***No Vancomycin powder*** (control)

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

- Centre
- Urgency of operation (Elective* OR Emergency)
- Indication for operation (Primary operation OR re-operation)
- Age (12 - <16 OR ≥ 16)

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

## 7.2 Blinding – Additional pillar-specific measures

Participants in the Neurosurgery pillar will be blind to the intervention(s) received. No additional measures to ensure blinding will be implemented within the Neurosurgery Pillar as all interventions are intra-operative and under the skin so should not be evident to the patient or any staff caring for the patient post-operatively.

# 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
- Diabetic control
- Use of a standard three-stage WHO Surgical Safety Checklist.

## 8.1 Standard care

**STANDARD OF CARE FOR CRANIOTOMY;**

- All patients will have some form of antiseptic skin preparation used (usually either betadine or chlorhexidine or both) and this will continue as per surgeon standard care
- Hair shaving will vary by surgeon preference
- All patients will receive pre/intra-operative antibiotic prophylaxis which will be given as per each site's standard policy for intra-cranial procedures

- The use of skin coverings, Raney clips, incision type and size will vary by site and operation and will be determined by the operating surgeon
- At the end of the operation, the wound will be closed in layers in a standard fashion and the skin will be closed with either clips or sutures. The wound will be cleaned and any combination of antiseptic spray, steristrips, dressing or no dressing may be used as per surgeon preference.

## 8.2 Trial interventions

**Intervention 1: Bone flap stored in aqueous betadine (10% Povidone-Iodine) versus saline**

Once the craniotomy has been performed and the bone flap lifted off, it will be put into a bowl/dish and submerged in either saline or aqueous betadine (as per randomisation allocation). It will remain in this fluid for the rest of the operation until the surgeon is ready to re-implant the bone flap at which point it will be removed to enable securing of screws/mini-plates and placed back into the participant. It can be washed in saline prior to re-insertion, but not in betadine if the participant was randomised to the saline arm.

**Intervention 2: Large volume (>1L) wound irrigation prior to closure (versus standard practice).**

Once the bone flap has been replaced and secured and the surgeon is ready to start closing the muscle/superficial layers, a large volume wash of a minimum of 1L of warm saline will be used to irrigate the wound. In the standard practice arm, the surgeon can choose to wash the wound at this stage with as much or as little saline as per their standard practice and this does not need to be measured.

**Intervention 3: Topical Vancomycin (500mg) powder versus none.**

Once the muscle and/or galea has been closed but prior to skin closure, the vancomycin powder (500mg) **WILL NOT BE RECONSTITUED** as per the manufacturer's instructions but will **be applied directly** to the wound edges.

500mg of vancomycin will be placed topically on the wound edges for the intervention arm. It will be spread out evenly across the length of the wound and a swab may be used to pat it down into the wound. The skin will then be closed in the standard fashion.

In the standard care arm no powder will be used and the skin will be closed in the standard fashion.

## 8.3 Contraindications

Specific contraindications to each included intervention are:

**Intervention 1:** allergy or known hypersensitivity to aqueous betadine

**Intervention 2:** N/A

**Intervention 3:** Known allergy to vancomycin or patients with previous or current hearing loss

### 8.3.1 Concomitant medication(s)/intervention(s)

Not applicable as all medications used are topical and not considered to interact with systemic medications.

### 8.3.2 Prohibited medication(s)/intervention(s)

Not applicable as all medications used are topical and not considered to interact with systemic medications.

## 8.4 Intervention modification or discontinuation

No intervention modifications or discontinuation is anticipated. All interventions are of single use during surgery. All interventions have been previously used in cranial neurosurgery .

## 8.5 Cessation of treatment/ Continuation of intervention after the trial

There is no indication for the cessation or continuation of the interventions after the trial since betadine, saline wash and vancomycin interventions are only applied intra-operatively.

## 8.6 Intervention supply and storage

### 8.6.1 Intervention supplies

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

**Intervention 1: Aqueous betadine**

Aqueous betadine will be supplied from routine hospital stock.

**Intervention 2: Large volume wound irrigation (Saline)**

This is standard hospital stock.

**Intervention 3: Topical vancomycin (Vancomycin 500mg vial iv powder single dose)**

Topical vancomycin will be obtained via routine hospital stock. Participating pharmacies will be requested to ringfence stock for trial use only.

### 8.6.2 Packaging and labelling

Intervention 1: aqueous betadine and intervention 2 large volume wound irrigation (saline) are not IMPs and are from standard hospital stock.

Intervention 3: topical vancomycin (vancomycin 500mg vial iv powder single dose) is taken from standard hospital stock but will have trial-specific labelling.

### 8.6.3 Intervention storage

The theatre teams will store products (*Aqueous betadine, Saline and Vancomycin)* 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 Intervention recalls

In the event that a product used as an intervention within the trial is recalled by the manufacturer, the site teams should follow their recall SOP.

## 8.7 Accountability

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

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

# 9. PILLAR SPECIFIC ADVERSE EVENT REPORTING

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

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

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

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

Any SAEs **NOT** listed in Sections 11.5.1 and 11.5.2 of the MASTER Protocol 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.

Within this Pillar, the adverse events that require expedited reporting are:

**Table 3 - SAE that require expedited reporting**

| Expected 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 | |

*Allergic reaction to any of the interventions:

- Aqueous betadine (10% Povidone-iodine)
- 500mg vancomycin.

**Any other SAEs not listed in Sections 11.5.1 and 11.52 of the MASTER protocol require expedited reporting to the trial office.**

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

## 9.2 Reference Safety Information Document

The Reference Safety Index (RSI) for the Neurosurgery Pillar within the ROSSINI-Platform trial is Section 4.8 Undesirable Effects of the SmPC for vancomycin (**Vancomycin 500 mg powder for concentrate for solution for infusion, Hameln Pharma Ltd).** This should be referred to for all safety events experienced by participants within the Neurosurgery Pillar as appropriate.

# 10. REFERENCE LIST


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# 11. APPENDIX