TRIAL PROTOCOL

ROSSINI 2: Reduction Of Surgical Site Infection using several Novel Interventions

A Phase III, multi-arm, multi-stage (MAMS), pragmatic, blinded (patient and outcome assessor) multicentre, randomised controlled trial (RCT) with an internal pilot, to evaluate the use of three in-theatre interventions, alone or in combination, to reduce SSI rates in patients undergoing abdominal surgery.

This protocol has regard for the HRA guidance and is compliant with SPIRIT.

Version Number:	**1.0**
Version Date:	**02 December 2018**

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

Protocol Development

Funding and Support in Kind	
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This is an investigator-initiated and investigator-led trial. The funders of the trial have no role in trial design, data collection, data analysis or data interpretation.	

Suppliers	
Becton Dickinson UK Ltd (BD)	Supplier of 2% Alcoholic Chlorhexidine skin prep [SKIN PREP]
3M United Kingdom PLC	Supplier of Iodophor-impregnated incise drape [DRAPE]
SERB	Supplier of Gentamicin-impregnated implants [SPONGE]

Protocol Sign Off

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential 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 study publically 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 planned in this protocol will be explained.

Trial Name:	**ROSSINI 2**
Protocol Version Number:	Version 1.0
Protocol Version Date:	02 December 2018
CI Name:	Mr Thomas Pinkney
Trial Role:	Chief Investigator
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement:

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

Compliance statement:

This protocol describes the ROSSINI 2 trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the ROSSINI 2 trial.

The study will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the General Data Protection Regulations, and the principals of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. 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.

PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential 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.

This protocol has been approved by:

Trial Name:	**ROSSINI 2**
Protocol Version Number:	Version 1.0
Protocol Version Date:	02 December 2018
PI Name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

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

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Trial website	<insert web address>

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Clinicaltrials.gov reference number	< reference number >
IRAS reference number	247285

ABBREVIATIONS

Abbreviation	Term
AMR	Antimicrobial Resistant
BCTU	Birmingham Clinical Trials Unit
CCG	Clinical Commissioning Groups
CDC	Centers for Disease Control and Prevention
CHaRT	The Centre for Healthcare Randomised Trials
CHG	Chlorhexidine Gluconate
CQUIN	Commissioning for Quality and Innovation
CRF	Case Report Form
DCF	Data Clarification Form
DM(E)C	Data Monitoring (and Ethics) Committee
GCP	Good Clinical Practice
GP	General Practitioner
GRIPP	Guidance for Reporting Involvement of Patient and the Public
ICF	Informed Consent Form
ISF	Investigator Site File
MAMS	Multi-arm, Multi-stage
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
PIS	Participant Information Sheet
POMR	Perioperative Mortality Rate (POMR)
PPI	Patient and Public Involvement
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	Research Governance Team

RUSAE	Related Unexpected Serious Adverse Event
SSI	Surgical Site Infection
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UHB	University Hospitals Birmingham
UoB	University of Birmingham
WHO	World Health Organization
WHQ	Wound Healing Questionnaire

DEFINITIONS

Term	Abbreviation	Description
Quality Management System	QMS	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event		An event which resulted from the administration of any of the research procedures.

Term	Abbreviation	Description
Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect Or is otherwise considered medically significant by the Investigator
Unexpected and Related Event		An event which meets the definition of both an Unexpected Event and a Related Event
Unexpected Event		The type of event that is not listed in the protocol as an expected occurrence.
Related Unexpected Serious Adverse Event	RUSAE	An SAE occurring to a research participant which in the opinion of the Chief Investigator was: - 'Related' that is, it resulted from the administration of any of the research procedures, and - 'Unexpected' that is, the type of event is not listed in the protocol as an expected occurrence. Medical and scientific judgement must be exercised in deciding whether an event is serious.
Source documents		All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the

Term	Abbreviation	Description
		reconstruction and evaluation of the trial
Birmingham Clinical Trials Unit	BCTU	The co-ordinating centre for the trial.
EQ-5D-5L		A standardized instrument for use as a measure of health outcome.
SKIN PREP		2% alcoholic chlorhexidine skin preparation provided by Carefusion/BD.
DRAPE		Iodophor-impregnated incise drape provided by 3M.
SPONGE		Gentamicin-impregnated implants/ sponge provided by SERB.

TRIAL SUMMARY

Title

ROSSINI 2 - Reduction **O**f **S**urgical **S**ite **I**nfection using several **N**ovel **I**nterventions

Primary Objective

To determine whether three specific in-theatre interventions, alone or in combination, result in decreased rates of surgical site infection (SSI) up to 30 days post operation in adult patients undergoing abdominal surgery.

Trial Design

Multi-arm, multi-stage (MAMS) pragmatic, multicentre, randomised controlled trial, with an internal pilot, exploring the use of three separate in-theatre interventions, used alone or in combination, to reduce SSI. A non-factorial design with allocation of various combinations of the three interventions to be used during the same operation, via seven possible intervention arms plus a control arm initially.

Trial Setting

10 local NHS hospitals will participate in the pilot phase of **ROSSINI 2** and at least 60 NHS hospitals in the UK will participate in the main phase of **ROSSINI 2.**

Participant Population and Sample Size

Approximately 6610 patients will be required to detect a 5% absolute risk reduction in the intervention arm(s) (15% to 10%) with 85% power.

Key Eligibility Criteria

Inclusion Criteria

Patients 16 years or older, undergoing abdominal surgery of any level of contamination, both emergency and elective (open or laparoscopic extraction site) with a planned incision of at least 5cm are eligible. Patients must be able and willing to give written informed consent.*

Exclusion Criteria

Patients with a previous laparotomy within 3 months prior to randomisation will be excluded.

**Patients with a new or documented allergy/intolerance to any of the study interventions (chlorhexidine, iodine, collagen or gentamicin) will not be randomised to an arm containing this intervention, but will still be eligible for recruitment to other arms of the study. Patients with end-stage renal failure where gentamicin administration would otherwise be contra-indicated (according to local policy) will not be randomised to arms containing the gentamicin-impregnated sponge.*

Interventions

Three health technologies will be assessed versus their control arms (standard care):

1. 2% alcoholic chlorhexidine skin preparation, versus any other standard skin preparation
2. Iodophor-impregnated incise drape, versus no drape
3. Gentamicin-impregnated implants/ sponge at closure, versus no implant

Outcome Measures

Primary: Surgical site infection(s) up to 30 days post operation will be assessed by a trained blinded assessor, by patient's self-report and defined according to the internationally accredited Centers for Disease Control and Prevention criteria (CDC).

Secondary:

- 30-day postoperative mortality rate (POMR).
- 30-day postoperative complication rate (Clavien-Dindo classification).
- Serious Adverse Events up to 30 days.
- Length of hospital stay after surgery as measured from the date of surgery to the date of discharge.
- Hospital re-admission for wound related complications within 30 days.
- Occurrence of unplanned wound reopening and/or re-operations within 30 days post-operation.
- Preference-based Quality of Life (QoL) measure (EQ-5D-5L) at Baseline, Day 7 (or discharge) and Day 30.
- Cost effectiveness (Health utility questionnaire)

Sub Study Objective

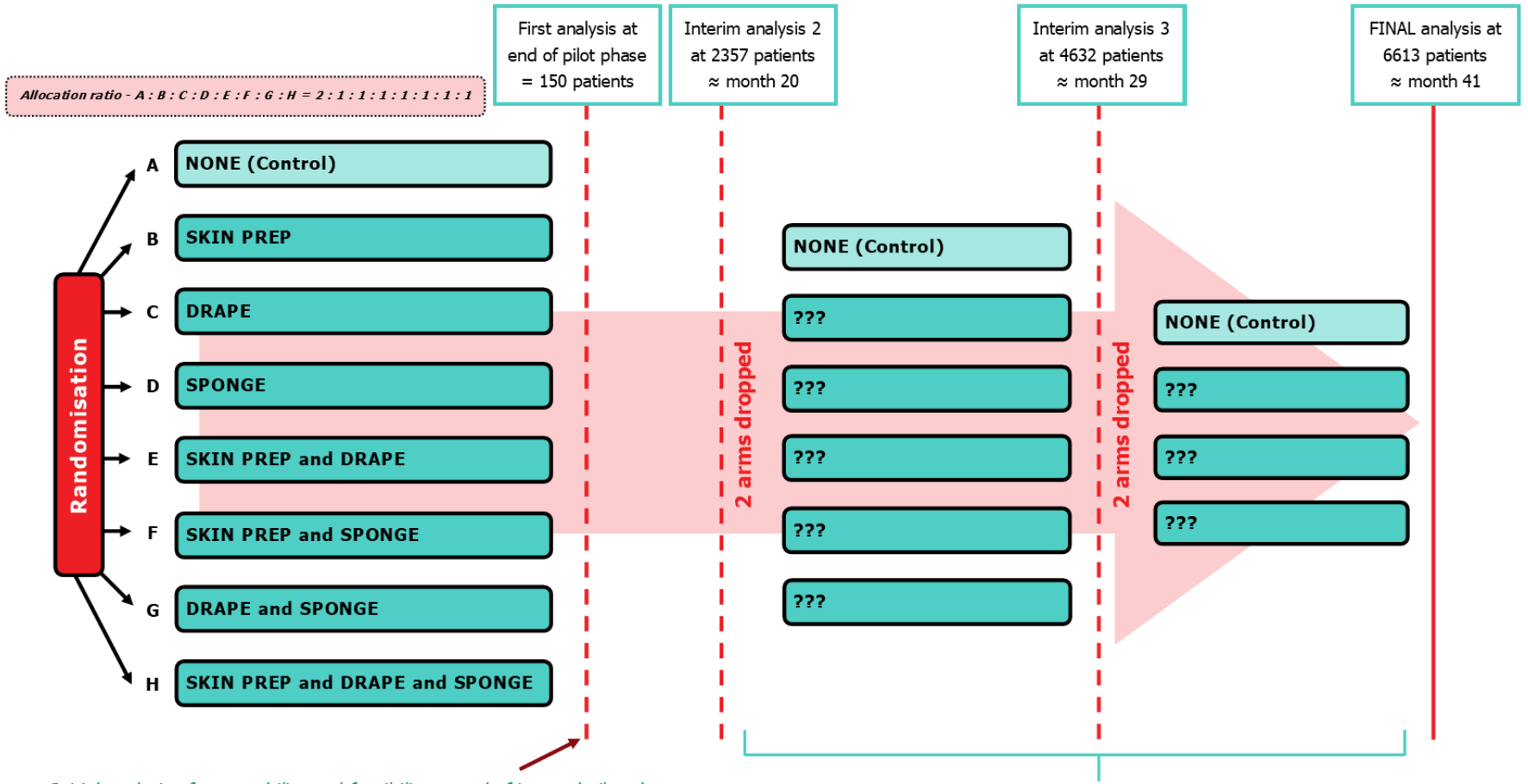
- Is there microbiological ratification of the clinical findings in terms of pathogenic organisms prevented/not prevented by use of the interventions or combinations of interventions?

TRIAL SCHEMA

Intervention 1 - 2% alcoholic chlorhexidine skin preparation [SKIN PREP]

Intervention 2 - Iodophor-impregnated incise drape [DRAPE]

Intervention 3 - Gentamicin-impregnated collagen implant/ sponge [SPONGE]



Initial analysis of acceptability and feasibility at end of internal pilot phase. Modifications made to arms if necessary. Second internal pilot can be requested by DMEC if concerns over arm adherence/ acceptability or overall recruitment rates.

STOP/ GO decision to drop arms dependant on any combination of:

A. Clinical effectiveness

B. Adherence to arm allocation

C. Clinician Acceptability

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1. BACKGROUND AND RATIONALE

1.1. Background

1.1.1. Surgical site infection after abdominal surgery

Surgical site infection (SSI) is a significant problem for patients and the health service, but is potentially preventable. At least 5% of patients undergoing a surgical procedure develop an SSI; with over 4 million operations in the UK annually this represents a minimum of 200,000 patients affected (3). At an average cost of £3500 per SSI, it has been estimated that SSIs currently cost the NHS around £700 million per year (4-6), largely through prolonged postoperative inpatient stay and additional inpatient and outpatient treatment costs (7, 8).

It is increasingly recognised that SSI incidence is widely underreported. Traditional monitoring relies heavily on passive surveillance with minimal review after discharge, but at least 60% of SSIs present in the community after discharge. Out of hospital SSI events are therefore often unaccounted for (9). With the increase of enhanced recovery programmes and shorter lengths of stay, the proportion of SSIs presenting outside of hospital has increased further. Rates of SSI vary significantly between different types of surgery, but is particularly prevalent in abdominal operations; as many as one in four patients get an SSI when the operation involves the bowel (10).

1.1.2. Impact of surgical site infection

There is a significant health need for research to address the problem of SSI, with benefit for both patients and the NHS. SSI is associated with considerable morbidity, a reduction in quality of life and increased healthcare costs, and places a significant burden on healthcare systems and individuals. It has also been shown to be an independent predictor of mortality (11) and in 2002 there were 8,205 deaths in the US due to SSI, accounting for 8% of all deaths caused by a nosocomial infection (12, 13). Development of an SSI significantly increases duration and cost of patient hospitalisation, predominantly due to re-operation, additional nursing care and drug treatment costs (4-6). There is an additional societal burden of SSI, delaying return to work or normal activity and increasing care burden (7).

1.1.3. Strategies to reduce SSI

Preventing SSI is a complex process which is affected by interventions throughout the surgical care pathway. SSI reduction measures when bundled, or poorly implemented can be ineffective (14) or even increase SSI risk (15). A large proportion of SSIs are known to be caused by wound contamination by endogenous bacteria from the patient's skin, or cross-contamination from mucous membranes, hollow viscera, free pus or bowel contents (16). This has resulted in the development of many intraoperative interventions to try to decrease this contamination and thereby decrease SSI rates. Unfortunately, clinical studies exploring the efficacy of many of these interventions are often underpowered or poorly designed, or used in low risk groups leaving uncertainty if they are clinically and cost-effective. **ROSSINI 2** aims to study simple biologically plausible interventions that may decrease SSI rates after abdominal surgery, but currently lack evidence in controlled studies. In this high risk group,

SSI reduction benefits seen will bring the greatest rewards, both clinical and financial, and findings should be generalisable to other types of surgery.

1.1.4. ROSSINI 1 trial

The ROSSINI 1 trial recruited 760 patients from 21 UK centres from 2010 to 2012 (1). ROSSINI 1 established several pathways that will support the delivery of a trial of multiple intraoperative interventions aimed at SSI reduction:

- Data collection systems for blinded wound reviews, both before and after discharge, as well as the patient-reported wound survey to cover the intervening period.
- Wound assessment online training resources, to educate and accredit wound assessors to the same standards (17). This reduces inter-rater variability and ensuring an inherently subjective endpoint is as reliable as possible.
- In-theatre randomisation, thereby helping to maintain blinding of outcome assessors, and minimising drop-out and treatment crossover.
- Created a national network of research-active surgical trainees, with GCP training and the skillset to recruit patients to other randomised trials (18, 19).

1.2. Trial Rationale

1.2.1. Benefits to patients

SSI is the most common nosocomial infection worldwide (20) and effects patients across all settings (21). It delays hospital discharge and return to work, causes significant pain and discomfort and has a significant and lasting impact on patients' quality of life (22). SSI can have serious consequences; patients are twice as likely to die as those without SSI and around one third of postoperative deaths are attributable, at least in part, to SSI (6). Antimicrobial resistant infections (AMR), the focus of a recent *Lancet* commission, are increasing at an alarming pace, and pose a great threat to patients and healthcare systems alike (23). In 2016, an international cohort study suggested that one fifth of SSI (21.6%) were resistant to the prophylactic antibiotic used at time of surgery (16). Effective SSI prevention strategies that can be used across diverse settings will reduce the burden of antibiotic use and mitigate the global impact of AMR.

1.2.2. Benefits to the health service

This major, multicentre, multi-arm, multi-stage (MAMS) trial with the opportunity to cease (and introduce) arms would be the first of its kind in a surgical setting. In addition to generating new knowledge in our primary research area, by utilising this advanced design in the context of our relatively simple primary endpoint of SSI, it will also pave the way for future efficient and rapid trials in other aspects of surgical care. This major trial has a broad inclusion criteria and will be easy to recruit to at every UK hospital where elective or emergency operations take place. It will be disseminated and driven both by surgical trainees and Clinical Research Network staff and will involve participation from many new surgical investigators at both consultant and trainee level. Surgeons undertaking abdominal surgery of any type will be able to participate. It is likely that this trial would serve to further improve the quality and

quantity of surgical clinical research in the UK and in so doing significantly benefit patients into the future.

1.2.3. Why the trial is needed now

The detrimental impacts of SSI have been the subject of heightened interest over the past decade, and are the subject of an updated NICE quality standard published in 2017 (24). This document describes SSI as a high-priority area for quality improvement and suggests that commissioners may adopt SSI rates as a CQUIN (Commissioning for QUality and INnovation) target. We know that at least 10 Clinical Commissioning Groups (CCGs) have gone on to include SSI reduction as a CQUIN target in this manner (25). SSI is also the target of a 2017 national consultation and audit process targeted at looking at reduction in SSI practice and highlighting areas for improvement in quality of care (26, 27). SSI will remain an area of significant and sustained attention for both clinicians and providers, further strengthening the relevance and importance of this trial.

1.2.4. Justification for participant population

Recent high-quality prospective registries and randomised trials in abdominal surgery with comprehensive post-discharge follow-up have shown consistently high SSI rates of 22-26% (1, 15, 28-40). By targeting this high risk population, where operative field contamination is common a clinically significant benefit is most likely to be identified.

1.2.5. Justification of a multi-arm multi-stage design

SSI prevention lends itself well to an adaptive or multi-arm, multi-stage (MAMS) trial design, because the primary outcome result is, by definition, available 30 days after the intraoperative intervention is applied. Interim analyses can exploit this short timeline to create an efficient trial that will evaluate several interventions (both individually and in combination) under a single umbrella structure. This decreases both the time and cost investment necessary to simultaneously determine if several non-bundled interventions are effective (41-44). Determining small incremental benefits will be slow and difficult to achieve. This trial design allows exploration of interactions between interventions, which each have a different biological mechanism in this multifactorial process.

1.2.6. Choice of interventions and controls

A series of systematic reviews have been undertaken and combined with current national and international guidelines to select the interventions assessed in this trial, taking into account current NHS policy. The three relevant guidelines to this study are:

- WHO Surgical Site Infection prevention (45)
- Centers for Disease Control (CDC) and Prevention Guidelines for the prevention of SSI (46)
- NICE Clinical Guideline 74: Prevention and treatment of SSI (24)

Three health technologies will be assessed in **ROSSINI 2**. All of the interventions chosen have demonstrated the potential to decrease SSI, yet lack the evidence base to be

recommended in international guidelines and do not form current standard practice in the UK. A prospective one-week snapshot audit of current usage of the study interventions at five NHS hospitals confirmed that none of them were currently in routine use (47). After clinical equipoise was confirmed, all eligible interventions were shortlisted and were prioritised according to their perceived potential to impact on SSI rates. The three interventions chosen impact different phases of perioperative care and as such can be used either in isolation or conjunction with each other and although there may potentially be interaction between the interventions (positive or negative) they appear to be mechanistically disparate.

(1) 2% alcoholic chlorhexidine skin prep

Mechanism: A broad-spectrum antiseptic to clean and prepare the skin prior to surgery.

Supplier: Carefusion/BD

Guidelines:

- WHO recommends alcoholic chlorhexidine-based antiseptic solution for surgical site skin preparation in patients undergoing surgical procedures, based on meta-analyses of low quality evidence.
- CDC recommends that intraoperative skin preparation should be performed with an alcohol-based antiseptic agent unless contraindicated.
- NICE recommends using either an alcohol povidone-iodine or alcoholic chlorhexidine; however, recognises that the evidence base remains uncertain.

Evidence base: Published meta-analyses describe 11 randomised controlled trials (RCTs) comparing antisepsis with chlorhexidine or povidone-iodine across 6385 patients. Chlorhexidine reduced SSI compared with povidone-iodine (pooled RR=0.70; 95% C.I.=0.60-0.83)(48, 49). This included a large 2010 RCT of 849 mixed speciality patients showed significantly lower SSI in the chlorhexidine alcohol group than in the povidone-iodine group (50). However, this trial has been criticised for a non-pragmatic control group; our survey data suggests that few hospitals use 2% alcoholic chlorhexidine routinely in abdominal surgery (47).

(2) Iodophor-impregnated incise drapes

Mechanism: A thin impregnated plastic sheet applied to the prepared skin prior to incision to maintain sterility.

Supplier: 3M Infection Prevention

Guidelines:

- WHO conditionally recommends not to use plastic adhesive incise drapes with or without antimicrobial properties, based on lack of evidence of effectiveness from one low quality RCT and one very low quality quasi-RCT.

- CDC makes a weak recommendation that plastic adhesive drapes with or without antimicrobial properties are not necessary for the prevention of SSI.
- NICE does not recommend the use of incise drapes due to lack of evidence for effectiveness. If an incise drape is required to maintain the integrity of the operative site, NICE recommends the use of an iodophor-impregnated drape unless the patient has an iodine allergy.

Evidence base: Analysis of a subset of a Cochrane review showed no effect from impregnated adhesive drapes on the SSI rate (RR 1.03, 95% CI 0.06-1.66, p=0.89) but this included only 2 RCTs, only one of which was in abdominal surgery and was nearly 30 years ago (51, 52). A more recent non-randomised trial in clean-contaminated abdominal surgery showed significant reduction in SSI (12.1% to 3.1%; p=0.0096). Surgeons are known to be keen on using the device as it serves to maintain the integrity of the operative field by sticking drape edges down. Impregnated incise drapes are part of SSI prevention bundles currently being used in major UK and US hospitals (53).

(3) Gentamicin-impregnated implants/ sponge

Mechanism: Small absorbable sponges placed into the wound at the time of closure which deliver high concentrations of antibiotic locally to kill pathogens present that may go on to cause SSI.

Supplier: SERB

Guidelines:

- WHO and CDC do not make a recommendation on the use of gentamicin impregnated sponges.
- NICE does not make a recommendation for gentamicin-collagen implants in abdominal surgery but make a provisional recommendation for their use in cardiac surgery. However, NICE express concerns about potential adverse effects of topical antibiotics on microbial resistance, and request more evidence from large, pragmatic trials with longitudinal assessment of microbial resistance.

Evidence base: A published meta-analysis of 15 RCTs comparing use of the implant versus placebo or nothing across all types of surgery in 6979 patients (54). Overall the implants significantly reduced SSI (OR 0.51; 95% CI 0.33-0.77; p=0.001) but the majority of trials were in thoracic or pilonidal surgery. A large RCT specifically exploring their use in abdominal (colorectal) wounds found an apparent increase in SSI rates in the intervention arm, but concerns about the way the implant was used have been raised (55, 56). A Cochrane review of the intervention is still in analysis but will expect to show ongoing equipoise in abdominal surgery (57).

2. AIMS AND OBJECTIVES

ROSSINI 2 is a multi-arm, multi-stage (MAMS) multicentre randomised controlled trial (RCT) with a 6-month internal pilot. The aims and objectives for the pilot and the main trial are defined separately below.

2.1. Internal Pilot

2.1.1. Aims

The aims of the internal pilot trial are to assess:

1) if recruitment to the randomised interventions is feasible
2) adherence to randomised intervention allocation
3) if patient follow-up can be completed within protocol-specific timeframes.

The internal pilot will recruit 150 patients across 10 sites.

2.1.2. STOP/ GO Criteria

The STOP-GO criteria will be assessed at 6 months post-start of recruitment. The following criteria will be used to determine the feasibility of trial progression:

- **Recruitment:** At least 6 of the 10 pilot trial sites will achieve an average recruitment of 4 patients per month by the end of the pilot phase.
- **Adherence:** Investigators' adherence to arm allocation within all three intraoperative interventions and their combinations must be at least 80%.
- **Follow-up:** Timely completion and submission of Case Report Forms (CRFs) is crucial to allow interim analyses for the adaptive design. The ability to complete blinded, in-person primary outcome assessments at 30 days post operation and data submission within 60 days of randomisation should be at least 70% by the end of the pilot phase.

At the end of the pilot phase, the **ROSSINI 2** Trial Steering Committee (TSC) will review the data and make recommendations on whether progression to the full phase is feasible. If any of the STOP-GO criteria have not been met, the TSC may recommend a second 6-month internal feasibility phase to verify recruitment rates are feasible and deliverable, or that measures put in place have improved the intervention adherences rates.

- Low recruitment in the pilot will help guide the number of centres that need to be opened for the full trial.
- If any arm does not meet a pre-specified adherence rate of 80%, this will be addressed via investigators' meetings with a discussion of issues and agreement of logistical and/or educational modifications made.

If a second pilot phase is required, the TSC will review the data again after another 6 months of recruitment:

- Any arm with less than 80% adherence will be dropped.
- If the overall recruitment targets are not met by the end of month 12 of recruitment, recruited patients will continue to be followed up. All other

recruitment will cease and the data collected will be analysed for all patients recruited up to that point.

2.2. Main Phase III Trial

2.2.1. Primary Objective

To determine whether three specific in-theatre interventions, used alone or in combination, result in decreased rates of surgical site infection (SSI) up to 30 days post operation in adult patients undergoing abdominal surgery.

2.2.2. Objectives

2.2.2.1. Clinical

- Do the intraoperative interventions alone, or in various combinations (within seven possible intervention arms and one control arm) reduce the overall rate of SSI after abdominal surgery?

- Is the efficacy of the intervention/treatment arm dependent upon;
  - degree of wound contamination (clean, clean-contaminated, contaminated, dirty)?
  - patient comorbidity (e.g. diabetes, smoking, obesity)?
  - duration of operation?
  - stoma formation?

- Do the intraoperative interventions:
  - have an acceptable safety profile?
  - reduce the rates of wound complications?
  - reduce the rates of mortality?

2.2.2.2. Economic

- Does the use of the interventions, either alone or in combination:
  - improve health-related QoL?
  - reduce the length of stay in hospital?
  - reduce wound complication related hospital re-admissions?
  - reduce the occurrence of unplanned wound reopening and/ or re-operations?
  - are cost-effective?

2.3. Sub Study

2.3.1. Mechanistic

- Is there microbiological ratification of the clinical findings in terms of pathogenic organisms prevented/not prevented by use of the interventions or combinations of interventions?

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

A Phase III, multi-arm, multi-stage (MAMS) pragmatic, blinded (patient and outcome assessor) multicentre, randomised controlled trial (RCT) with an internal pilot, to evaluate the use of three in-theatre interventions to reduce SSI rates in patients undergoing surgery with an abdominal incision. Non-factorial superiority design with allocation of various combinations of the three interventions to be used during the same operation, via seven possible treatment arms plus one control arm initially.

3.2. Trial Setting

10 local NHS hospitals will participate in the pilot phase of **ROSSINI 2** and at least 60 NHS hospitals in the UK will participate in the main phase of **ROSSINI 2.**

3.3. Identification of participants

Adults undergoing abdominal surgery will be identified for recruitment in both elective and emergency settings.

- In the elective setting patients will be identified via clinics, admission logs, theatre booking systems and multidisciplinary team meetings.
- In the emergency setting patients will be identified from the emergency department, surgical assessment units and theatre booking systems.

Embedding surgical trainees, research nurses and consultant surgeons within the site teams will maximise the ability to screen for eligible patients.

3.4. Patient and public involvement

This trial has been developed in partnership with patient representatives and service users, from the Birmingham Surgical Research Patient Forum. Three patient representatives sit on the Trial Management Group (TMG) providing input into aspects of trial design and delivery, patient-facing documentation such as Patient Information Sheets (PIS) and Informed Consent Forms (ICF). These individuals will directly represent patients and their views prospectively during all phases of the trial.

All PPI involvement in this trial will be reimbursed according to the INVOLVE guidelines, and their participation reported according the GRIPP2 framework (58).

3.5. Sub-studies

A sub-study is planned in parallel to this MAMS trial to determine if there is microbiological ratification of the clinical findings in terms of pathogenic organisms prevented or not prevented by use of the interventions or combinations of interventions. This is further detailed in Section 19 of this protocol.

3.6. Assessment of Risk

This trial is categorised as:

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

The specific three interventions being studied in the trial are already being used by a small number of surgeons nationally and internationally. They are all commercially available and approved for use in the UK. In the absence of level 1 evidence, current behaviours for SSI reduction practice are influenced by surgeon experience and hospital policies governing local availability. As a pragmatic trial, **ROSSINI 2** is designed to have minimal impact upon a patient's standard clinical care and thereby enhance recruitment and adherence to arm allocation, whilst maximising follow-up rates. We propose to randomise patients to receive adjunctive interventions in addition to standard care in an attempt to decrease their likelihood of developing a potentially serious post-operative complication. None of the interventions are known to cause harm and none will significantly increase the time of an operation or make it more technically difficult.

The only additional patient interactions within this trial are as follows:

(1) Pre-operative discussions about the trial and provision of PIS
(2) Consent and a QoL questionnaire (EQ-5D-5L) at baseline (pre-op)
(3) In-theatre randomisation
(4) Use of the intraoperative intervention(s), unless allocated to control arm
(5) An in-person (in-patient) wound review by a blinded, clinically trained observer and a QoL questionnaire (EQ-5D-5L) at Day 7 (or pre-discharge).
(6) Another in-person (out-patient) wound review by a blinded, clinically trained observer and a QoL questionnaire (EQ-5D-5L) at Day 30, with the intervening period covered by a patient self-reported wound healing questionnaire (to be completed at Day 30).

We intend to incorporate these into routine care pathways, such as introducing/discussing the trial at the pre-operative assessment clinic visit, consenting on the morning of surgery, the initial wound assessment whilst an inpatient and the final 30 day wound assessment during the standard postoperative follow-up outpatient visit where possible.

Before opening, all sites will receive trial-specific training, both on the logistical and operational aspects of the trial and in the correct use of the various interventions to ensure a standardised and optimal method of use. This will mitigate risk of harm through improper application, whilst being minimally disruptive to broader clinical practice at the site.

4. ELIGIBILITY

4.1. Centre and surgeon eligibility

Any centre performing emergency and/or elective abdominal surgery will be eligible to participate in **ROSSINI 2**. Sites entering the trial must not be routinely using these interventions and be willing to accept patients being randomised to receive (or to not receive) each of them, including combinations thereof. Surgeons must be willing to adhere to arm allocation and be willing to be trained in a standardised application technique.

4.2. Inclusion Criteria

- Patients undergoing colorectal, hepatobiliary, upper GI, urological, vascular, or gynaecological operations
- Patients undergoing abdominal operations (open or laparoscopic extraction site) with a planned incision of at least 5cm.
- Patients aged 16 years or older
- Patients able and willing to give written informed consent
- All contamination strata, including clean, clean-contaminated, contaminated or dirty surgery.
- Patients undergoing planned (elective or expedited) or unplanned (emergency) surgery.

4.3. Exclusion Criteria

- Previous laparotomy within 3 months prior to randomisation
- Patients with a new or documented allergy/ intolerance to any of the study interventions (chlorhexidine, iodine, collagen or gentamicin) will not be randomised to an arm containing this intervention, but will still be eligible for recruitment to other arms of the study.
- Patients with end-stage renal failure where gentamicin administration would otherwise be contra-indicated (according to local policy) will not be randomised to arms containing the gentamicin-impregnated sponge.

Participants who potentially fulfil the inclusion criteria for this trial must have their eligibility confirmed by an appropriately delegated member of the local research team with access to and a full understanding of the potential participant's medical history. If eligibility has been assessed and documented, then the process of obtaining informed consent may be delegated as appropriate and as documented on the **ROSSINI 2** Site Signature and Delegation Log.

Each individual patient should **not** undergo a second randomisation to **ROSSINI 2** within 30 days post-surgery and until the previously randomised wound has fully healed.

4.4. Co-enrolment

Participants 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 study.
Sites should contact the **ROSSINI 2** Trials Office to discuss co-enrolment. A list of trials in which patients can be co-enrolled is available on the **ROSSINI 2** website or from the **ROSSINI 2** Trial Office.

5. CONSENT

It will be the responsibility of the Investigator (or delegate) to obtain written informed consent for each participant prior to performing any trial related procedure. Consent may be taken by the local surgical consultant PI, other consultant surgeons or surgical registrars (with up-to-date GCP training) as delegated by the local PI and captured on the **ROSSINI 2** Site Signature and Delegation Log. Research nurses can also obtain consent if local practice allows and this responsibility has been delegated by the site PI and captured on the Delegation Log.

All eligible patients will be approached for recruitment to **ROSSINI 2**. A Participant Information Sheet (PIS) will be provided to facilitate this process.
Investigators will ensure that they adequately explain:

- That consent is sought for inclusion in a randomised controlled trial
- That the trial will compare different interventions aiming to reduce SSI rates
- That the interventions will be allocated at random
- What the trial will involve for the participant
- The anticipated benefits and potential risks of taking part in the trial
- That participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time.

The participant will be given an acceptable adequate amount of time to read the PIS and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions before signing and dating the latest version of the **ROSSINI 2** Informed Consent Form (ICF). The participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records.

The investigator (or delegate) will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's unique trial number (TRIAL ID) will be entered on the ICF and maintained in the ISF. In addition, if the participant has given explicit consent, a copy of the signed ICF will be sent by post to the Birmingham Clinical Trials Unit (BCTU) trials team for review.

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 participant and version number of ICF signed and date consent

received. In emergency situations where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local institution. Details of all patients approached about the trial will be recorded on the **ROSSINI 2** Patient Screening Log (held at site) and with the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

6. RECRUITMENT, ENROLMENT AND RANDOMISATION

6.1. Recruitment

Patients will be identified as potential participants at the time they are listed for surgery by a surgical trainee, consultant or nurse (with confirmation from a registered medical practitioner). It is envisaged that a majority of patients will be screened and recruited in four scenarios:

1. Surgery outpatient clinics, such as Colorectal, Upper GI, Hepatobiliary/ Pancreatic, Renal, Urological, Vascular and Gynaecology – by a Consultant or trainee surgeon when the patient is being booked for elective surgery.
2. Pre-assessment clinic – by a nurse or surgical trainee when the patient is being assessed for surgery.
3. Planned theatre lists – by a Consultant or trainee surgeon once a patient has been listed for surgery and arrives in hospital, i.e. at the time of admission for surgery.
4. In the emergency setting (assessment unit or emergency department) – by a Consultant or trainee surgeon when a decision to operate is made.

6.2. Screening

Potentially eligible patients will be screened and approached for entry into the trial by an appropriate member of staff delegated this responsibility on the **ROSSINI 2** Site Signature and Delegation Log. A **ROSSINI 2** Patient Screening Log should be prospectively maintained at each site using planned theatre lists, electronic theatre logs and the National Emergency Laparotomy Audit database.
The trial will be discussed with eligible elective patients pre-operatively, either in the outpatient clinic at the time of listing for surgery, or in the pre-operative assessment clinic where patients come routinely around 7-10 days prior to surgery.

In the emergency setting the trial will be discussed with patients at the same time as operative consent, once a definitive decision for surgery is made. Written information will be provided in the form of a Patient Information Sheet (PIS). In both settings, patients will be given as much time as possible to decide whether they wish to take part.

Informed consent for participation in the study will be obtained preoperatively and the **ROSSINI 2** Informed Consent Form will be signed by both elective and emergency patients; this will normally be in the same setting where the usual operation consent for the intended surgical procedure is also obtained.
After consent, patient-level demographic data will be collected in the **ROSSINI 2** BASELINE CRF and a baseline health-related, preference-based QoL assessment using the EuroQol EQ-5D-5L questionnaire should also be completed.

The proportion of participants who temporarily lack capacity to consent to trial recruitment due to their disease severity (i.e. undergoing emergency surgery) will be identified from the **ROSSINI 2** Patient Screening Log and they will not be able to participate in **ROSSINI 2** at the time. If a high proportionate of patients lacking consent during the pilot phase are identified then deferred consent will be considered for the main phase.

6.3. Randomisation

After eligibility has been confirmed and informed consent has been received, the patient can be randomised into the trial. Randomisation into the trial will occur in theatre around the time of induction of anaesthesia on the day of surgery and after eligibility has been confirmed and consent obtained. We have successfully developed this method across three other NIHR portfolio multicentre, trainee-led RCTs (1, 18, 19). This maintains concealment of each intervention (blinding) from ward staff, from any staff that may conduct the wound review and the patient, and minimises bias, attrition from crossover or drop-out.

There will be a secure online randomisation system (available at https://w3.abdn.ac.uk/hsru/ROSSINI2) and an automated telephone randomisation system (available at 0800 2802 307) both managed by a 3rd party (The Centre for Healthcare Randomised Trials (CHaRT) at The Institute of Applied Health Sciences at University of Aberdeen). Both systems will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

A **ROSSINI 2** RANDOMISATION FORM must be completed in order to randomise a patient. This form should be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form must be answered before a Trial Number can be given.

6.3.1. Randomisation methodology

Participants will be randomised at the level of the individual in a 2:1 (control:research) ratio to either control or one of the treatment groups. There will initially be seven possible treatment arms and one control arm to which a patient can be randomised (see Trial Schema). Each

arm will specify different combinations of the interventions that will be allocated and used during that specific operation. These interventions will be applied by the operating team as per the study protocol and each site will be given trial specific training during site set-up to ensure homogeneity (see Separate Appendix).

A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

- Centre
- Urgency (planned, unplanned)
- Predicted contamination (clean, clean-contaminated, contaminated, dirty)
- Stoma (yes – existing, yes – likely to be created during procedure, no - unlikely to be created during procedure)

The contamination level will be predicted by the operating surgeon before a skin incision is made, based on available clinical, radiological, endoscopic, biochemical or haematological parameters (60, 61):

- Clean – an incision in which no inflammation is encountered in a surgical procedure, without a break in sterile technique, and during which the respiratory, alimentary and genitourinary tracts are not entered (inclusion criteria for this study excluded this group);
- Clean-contaminated – an incision through which the respiratory, alimentary or genitourinary tract is entered under controlled conditions but with no contamination encountered;
- Contaminated – an incision undertaken during an operation in which there is a major break in sterile technique or gross spillage from the gastrointestinal tract, or an incision in which acute, non-purulent inflammation is encountered. Open traumatic wounds that are more than 12 to 24 hours old also fall into this category;
- Dirty – an incision undertaken during an operation in which the viscera are perforated or when acute inflammation with pus is encountered during the operation (for example, emergency surgery for faecal peritonitis), and for traumatic wounds where treatment is delayed, and there is faecal contamination or devitalised tissue present.

A 'random element' will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to a different intervention than they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU. Following randomisation, a confirmatory e-mail will be sent to the randomiser, the local PI and the trial coordinator.

Normal local policies for perioperative care, including patient warming, systemic antibiotic prophylaxis and venous thromboembolism will be followed, with completion of a standard three-stage WHO Surgical Safety Checklist (62). The operation will be carried out as normal, with use of the relevant 'recipe' of intraoperative interventions (if any) as per the randomised allocation. Immediately after the operation, the **ROSSINI 2** IN-THEATRE FORM will capture the intraoperative details and verify which interventions were utilised and, if there was deviation from the randomised allocation, why this occurred.

Investigators will keep their own study file log which links patients with their allocated trial number in the **ROSSINI 2** Patient Recruitment and Identification Log. The Investigator must maintain this document, which is not for submission to the Trials Office. The Investigator will also keep and maintain the anonymised **ROSSINI 2** Patient Screening Log which will be kept in the ISF, and should be available to be sent to the Trials Office upon request. The **ROSSINI 2** Patient Recruitment and Identification Log and **ROSSINI 2** Patient Screening Log should be held in strict confidence.

6.4. Informing the participant's GP

If the participant has agreed, the participant's GP should be notified that they are in **ROSSINI 2**, using the **ROSSINI 2** GP Letter. The GP will not be told the patient's group allocation.

6.5. Blinding

ROSSINI 2 is a double blind trial; both the patient and outcome assessor will be blinded to the intraoperative intervention(s). It is not possible to blind the operating surgeon to the intervention allocation.

The following measures will be taken to ensure concealment of the chosen intervention(s) (blinding):

- Randomisation in theatre after induction of anaesthesia
- The intraoperative interventions used will not be documented in the operation note or in the patient's notes. Only stickers indicating trial involvement and the procedure for unblinding will be provided in the patient's notes.
- The skin around the closed wound will be wiped clean using a wet sterile towel at the end of the procedure to prevent unblinding due to discolouration of the skin.
- Clinical follow-up will be conducted by a trained surgeon (Membership of the Royal College of Surgeons level or equivalent) or a trained member of the local research team who did not participate in the index procedure or surgery.

6.6. Unblinding

Patients will be unblinded upon request at the end of the study, which is once the final patient has completed 30-day follow-up and the database is locked.

Emergency unblinding will only be permitted for medical reasons (e.g. severe allergy), and coordinated by the BCTU Trials Office. In case of an out-of-hours emergency, the named operating surgeon and/or site PI should be contacted for the allocation and the **ROSSINI 2** site office should be notified at the earliest available opportunity.
Unblinded participants will continue to have outcome assessment up to 30 days postoperatively and the impact of this will be examined in a sensitivity analysis.

7. TRIAL INTERVENTIONS

7.1. Usual care and site requirements

Patients in **ROSSINI 2** will be randomised to one of eight arms (seven intervention(s) arms or one control arm). We will open approximately 60 research-active units with whom we have previously undertaken successful RCTs exploring intra-operative procedures (1, 18, 19). All of these centres have indicated that they are not routinely using these interventions and would be willing to exclude their use in the control arm.

As a pragmatic RCT, **ROSSINI 2** will not mandate a rigid set of parallel measures for the prevention of SSI as part of usual care in each trial centre, as this would limit wider generalisability of the findings. We will, however, stipulate that all sites opening for the trial should adhere to a minimum set of policies as per the NICE guidance CG74 (24) on the prevention of SSI, monitored using the **ROSSINI 2** IN-THEATRE FORM. This includes:

- The monitoring and maintenance of normothermia
- Hair removal, in theatre, immediately before the time of incision, using an electronic shaver (if required)
- Administration of empirically selected prophylactic antibiotics
- Use of a standard three-stage WHO Surgical Safety Checklist.

Some sites will undertake additional measures to try and reduce SSI as part of their routine patient care. Providing this does not impinge on any of the trial interventions this will be allowed to continue, in the interests of pragmatism, and will be captured regularly at a surgeon-specific (Trainee) level throughout the trial every twelve months as we recognise such behaviours and measures are likely to evolve throughout the duration of the trial. Participating surgeons at sites will be asked to complete an electronic questionnaire (using the REDCap system). This questionnaire will collect information on any changes to practice or new interventions employed during the course of the trial which may impact on the baseline SSI rates.

Before opening, all sites will receive trial-specific training on the logistical and operational aspects of the trial. All investigators will undergo a training and certification process that includes:

1. Watching a video outlining proper use of study interventions
2. Training on the correct use of the interventions by a member of the TMG or the local PI
3. Access to standardised 'training cards' for use in theatre as an *aide memoire* for the application of the intervention technique

This will ensure the correct use of the various interventions to ensure a standardised and optimal method of use. The training methods and materials are described in a separate Appendix.

7.2. Intraoperative interventions and comparators

Intervention 1: 2.0% Alcoholic Chlorhexidine Skin Prep *(BD Infection Prevention)*

This intervention describes the preparation of the intact skin incision site immediately prior to incision, using chlorhexidine gluconate (CHG) in an alcohol-based solution, providing durable sterilisation of the surgical field. Pre-prepared applicators will be available for use in this trial (ChloraPrep™ sticks, 2% CHG with 70% isopropyl alcohol, BD Infection Prevention).

To prepare the applicator:

- The ChloraPrep stick must be 'activated' by depressing the trigger.
- Ensure that the 2% alc. CHG is leeching into the sponge at the end of the ChloraPrep applicator.

To apply the 2% alc. CHG:

- Begin by cleaning the umbilicus using the provided sticks, saturated in the 2% alc. CHG solution
- Use the ChloraPrep applicator to begin preparing the surgical field, starting directly over the planned incision site
- Use a backwards and forwards or circular motion for 30-60 seconds over the surgical incision site before moving outwards towards the limits of the surgical field
- Use of a second applicator may be necessary in field sizes greater than 30cm x 30cm, if the operating surgeon deems this appropriate
- The prepared field must be outwith that of the operating field insight.

Before applying sterile drapes around the operating field:

- Manage any pooling by drying with a single, sterile towel or gauze
- Allow the 2% alc. CHG solution to dry for at least 2-3 minutes until the shiny surface changes to a matt effect on the prepared skin.

If further extension of the prepared field, or re-sterilisation of the operating field is required for any reason during the procedure, then a further ChloraPrep may be used. Specific training for the use of this intervention can be found in the Intervention Training Appendix.

Comparator 1: All patients undergoing an abdominal operation will have their skin prepared using some form of antiseptic skin preparation. Other commonly used agents include 0.5% chlorhexidine or povidone-iodine, in aqueous or alcoholic solution. Concentrations and volumes of preparations vary and can be mixed in theatre or used as pre-prepared solutions. **ROSSINI 2** will stipulate that any other skin preparation of the surgeon's choice may be used in the control arm. The **ROSSINI 2** IN-THEATRE FORM will collect specific details about variation in practice in the solution and method of preparation used in the control arm and ensure compliance to the randomised allocation.

Intervention 2: Iodophor Antimicrobial Incise Drapes *(3M Infection Prevention)*

This intervention describes the application of a single Iodophor Antimicrobial Incise Drape to be applied topically onto the prepared and draped surgical field by sterile, gloved members of the surgical team before the surgical incision is performed. Only after the skin preparation solution has dried completely can the incise drape be applied.

To prepare the drape for application:

- Remove the outer packaging
- Remove the paper overwrap
- Hold the drape with the printing on the handle facing up
- Separate the printed handle from the white handle

To apply the drape to the operating field, a two-person application is optimum, with one person standing on each side of the operating table:

- Person one holds the printed handle
- Person two pulls the white edged liner away from the printed handle
- Both persons should place their hands on the outer corners of the drape to maintain slight tension on the drape and keep the area wrinkle free
- Gentle unfold the drape over the operating field ensuring the limits of the drape are outwith the draped area of skin
- Stop unfolding the drape once the clear film is found on the white edge of the drape
- Smooth out any wrinkles with a sterile towel or gloved hand and ensure contact between the skin and the drape throughout
- Remove the remainder of the liner and the printed handle.

At the end of the procedure when the skin has been closed the incise drape should be removed from the operating field. As the drape is adherent, care must be taken to gently remove the drape form the patient's skin without causing abrasion or injury. Specific training for the use of this intervention can be found in the *Appendix*.

Comparator 2: In the control arm no incise drape (Iodine impregnated, or non-iodine impregnated) will be used.

Intervention 3: Gentamicin-impregnated implants/ sponges *(SERB)*

This intervention describes the implantation of Gentamicin-impregnated collagen implants at the time of fascial closure. Each sponge (10 by 10 cm) contains 280mg of collagen and 130mg of gentamicin. The sponges gradually degrade and the gentamicin solution permeates into surrounding tissues to create a high local antimicrobial concentration within the surgical wound.

To prepare the sponges for implantation:

- Remove outer packaging
- The implant can be cut to size through the sterile packaging whilst dry
- Ensure all gloved hands or instruments are free of blood before handling the implant
- Ensure the area to be treated is dry

To implant the sponges at the surgical site:

- Fascial closure will be completed according the surgeon's local practice
- One or two sponges should be inserted anteriorly to the fascia, along the full length of the incision
- Place light pressure to the implant until adhesion to the fascia is achieved
- This should occur immediately before closure of the surgical skin wound

Comparator 3: In the control arm no implant/sponge should be used and closure of the subcutaneous tissues and skin should be performed according the surgeon's standard practice.

7.3. Contraindications

The investigator must confirm the patient's eligibility to be randomised to each of the three interventions at the time of randomisation. If a patient is not able to receive one or two of the trial interventions, they will still be randomised to the remaining arm(s) and the reasons for this will be recorded on **ROSSINI 2** RANDOMISATION FORM and collated by the BCTU Trial Office.

Specific contraindications to each included intervention are:

Intervention 1: 2.0% Alcoholic Chlorhexidine Skin Prep *(BD Infection Prevention)*

- Do not use on broken skin or mucous membranes
- Do not use if the patient has a known sensitivity to Chlorhexidine or its constituent parts.

Intervention 2: Iodophor Antimicrobial Incise Drapes *(3M Infection Prevention)*

- Do not use if the patient has a known sensitivity to iodine.
- Do not attempt to defibrillate through the drape.

Intervention 3: Gentamicin-impregnated implants/ sponges *(SERB)*

The peak permitted serum-gentamicin concentration for a patient with normal renal function is 3-5mg/litre (63).

- Do not use in end-stage renal failure (per local hospital prescribing policy) or severe acute kidney injury (KDIGO stage 2/3, or acute requirement for renal replacement therapy).
- Do not use if the patient has a known sensitivity to gentamicin.
- Do not use if the patient is on concurrent gentamicin therapy via another route (a single dose of gentamicin at induction is permissible)
- Do not use if the patient has a known sensitivity to proteinaceous implants.

7.4. Accountability and Compliance Procedures

It is important to ensure that patients receive the allocated interventions and are applied with high fidelity during their operation to ensure the internal validity and reproducibility of the trial findings. Compliance to the arm allocation will be monitored using two mechanisms:

(1) The intervention(s) used in theatre will be collected on the **ROSSINI 2** IN-THEATRE FORM whilst also recording a unique product number for each allocated intervention;
(2) The number and resupply of trial interventions will be monitored by BCTU and assessed against expected level whenever a reordering request is required, or delayed.

BCTU will actively monitor adherence to arm allocations, exclusions of patients from arms of randomisation and resupply of trial interventions. None of the interventions are 'complex' to adopt, or involve a learning curve in their use, safety or effectiveness, so high fidelity monitoring of steps for implementation is not required. However, to ensure that all three

interventions are used in a homogenous and reproducible manner by all surgeons and sites, standardised training materials have been created and are detailed in a separate appendix.

7.5. Cessation of Treatment/ Continuation after the Trial

Two of the included interventions are both applied intraoperatively. Only Intervention 3: Gentamicin-impregnated implants/sponges at fascial closure *(SERB)* is left in situ postoperatively.
Patients who undergo re-laparotomy, wound exploration or explantation of the sponge will continue to be followed up to 30 days from the index procedure. The number of reoperation events will be collected as part of the **ROSSINI 2** RETURN TO THEATRE FORM (only report incidents that occur within 30 days post-surgery) and will be compared *a priori* between arms by the DMEC, in the interim analysis and the final analysis of effectiveness and cost-effectiveness.
If any trial intervention is withdrawn from the trial for a safety reason, randomised patients would be alerted immediately, appropriate, reparative safety measures taken and the patient would be asked whether they would like to continue to be part of the trial follow-up.

7.6. Treatment Supply and Storage

7.6.1. Treatment supplies

The manufacturer of each product will be responsible for the free provision of trial interventions to open trial centres. An initial supply of the interventions will be delivered to each site prior to site opening. It will then be the responsibility of the BCTU to arrange for resupply and delivery. The process for this will be explained during the Site Initiation Visit.
The boxes containing the trial interventions will be marked with a label "For **ROSSINI 2** Trial Use Only".

The industry partners supporting the provision of interventions for the **ROSSINI 2** Trial are:
Intervention 1: 2.0% Alcoholic Chlorhexidine Skin Prep
(BD Infection Prevention)

Intervention 2: Iodophor Antimicrobial Incise Drapes
(3M Infection Prevention)

Intervention 3: Gentamicin-impregnated implants/sponges
(SERB)

7.6.2. Packaging and Labelling

A unique product identity number will be provided as standard by the manufacturer for each intervention used within **ROSSINI 2.** This will be recorded on the **ROSSINI 2** IN-THEATRE FORM after the product is used, so to facilitate supply chain control and monitoring of compliance to arm allocation.

7.6.3. Storage and security

All interventions will be stored in a secure, clean, dry place free from damp at room temperature and within the supplied sterile packaging. The box will be marked "For **ROSSINI 2** Trial Use Only". No specific special requirements are required above the standard storage conditions of theatre products and refrigeration will not be necessary. All intervention materials that have expired will be sent back to the manufacturer. Any excess intervention material will be disposed of in the hospital's standard clinical waste bins as per local hospital protocol. Interventions must only be used for patients within the trial, randomised to the arm in question. Any centres using interventions outside the trial setting may be cautioned or asked to withdraw from the trial.

8. OUTCOME MEASURES AND STUDY PROCEDURES

8.1. Primary Outcome

8.1.1. Definition

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

The following CDC definition will be used in **ROSSINI 2** to identify deep incisional or superficial incisional SSIs:

1. The infection must occur within 30-days of the index operation

AND

2. The infection must involve the skin, subcutaneous, muscular or fascial layers of the incision

AND

3. The patient must have at least one of the following:

- Purulent drainage from the incision

  OR

- Wound opened spontaneously or deliberately by a clinician
  - **AND** the patient has at least one of: pain or tenderness; localised swelling; erythema or heat; fever (>38°C).

  OR

- Organisms are cultured from a culture taken from the wound using an aseptic technique

  OR

- Diagnosis of SSI by a clinician or on imaging

The interventions in the trial act locally on the wound and its surroundings to reduce contamination, both exogenous and endogenous, and thereby prevent the development of postoperative wound infection. Surgical site infection in **ROSSINI 2** encompasses both superficial and deep incisional wound infections. In practice, a deep incisional infection will manifest alongside a superficial one and can be viewed as a more severe subset of the latter. We will not seek to differentiate between deep and superficial SSI as our interventions seek to prevent both. The trial does not include organ space infections as an outcome measure; this is a rare complication when compared with superficial/deep infections and importantly, organ space infections are not likely to be affected (positively or negatively) by the interventions chosen for **ROSSINI 2**. We recognise the subjective component to SSI assessment and have sought to minimise this by applying centralised training and accreditation of the assessors using our previously developed online e-learning module. This approach was used successfully in the ROSSINI 1 trial (1).

8.2. Secondary Outcomes

- 30-day postoperative mortality rate (POMR).
- 30-day postoperative complication rate (Clavien-Dindo classification).
- Serious Adverse Events up to 30 days.
- Length of hospital stay after surgery as measured from the date of surgery to the date of discharge.
- Hospital re-admission for wound related complications within 30 days.
- Occurrence of unplanned wound reopening and/or re-operations within 30 days post-operation.
- Preference-based QoL measure (EQ-5D-5L) at Baseline, Day 7 (or discharge) and Day 30.
- Cost effectiveness (Health utility questionnaire).

8.2.1. Definitions and Timings

8.2.1.1. 30-day postoperative mortality rate

The 30-day postoperative mortality rate (POMR) is determined as death of a patient within the first 30 postoperative days, with day of surgery taken as day 0. POMR has been highlighted as a key performance indicator by the Lancet Commission on Global Surgery and recommended for use in all international clinical trials in surgery (67). In the ROSSINI 1 trial, with a similar participant inclusion criteria the POMR was 2.6% (1).

8.2.1.2. 30-day postoperative complication rate

The 30-day postoperative complication rate is determined as the highest level Clavien-Dindo grade complication measured in the first 30 postoperative days, with day of surgery taken as day 0. Any deviation from the normal postoperative course that has an adverse effect on the patient and is not either a treatment failure or sequel, is a complication. The Clavien-Dindo classification determines the severity of a complication based on the therapeutic consequence of that complication (68). This has been validated internationally across health settings with high reproducibility and low interrater variability.

Classification	Definition
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Requiring surgical, endoscopic or radiological intervention.
Grade 4	Life-threatening complication (including Central Nervous System complications) requiring critical care management.
Grade 5	Death of a patient.

Table 1. Clavien-Dindo classification of postoperative complications

8.2.1.3. Health-related, preference-based quality of life

QoL will be assessed using the widely validated EuroQol EQ-5D-5L questionnaire at baseline (preoperative), as an inpatient (day 7 or at discharge if sooner) and day 30 mirroring the timings of blinded wound assessment.

8.2.1.4. Cost-effectiveness

Cost effectiveness will be assessed using the Resource Usage Form to collect patient-level health resource usage both in primary and secondary care; reported in QALYs. This has been previously piloted in the ROSSINI 1 study (1).

8.3. Schedule of Assessments

Table 2. Schedule of Assessments for **ROSSINI 2**

Visit	Pre-operative (Elective and emergency surgery)	At surgery	Day 7 wound review (Wound Assessment Form to be completed as an inpatient on Day 7, or discharge if sooner) ±2 days	Day 30 wound review (Wound Assessment Form to be completed as an outpatient, between Day 30-37, ideally on Day 30)	Ongoing SSI (every 30 days until resolution)
Eligibility check	X				
Patient Information Sheet provided	X				
Written Informed Consent	X				
Reaffirm Consent		X	X	X	
Quality of life Questionnaire (EQ-5D-5L)	X		X	X	
Randomisation (RANDOMISATION FORM)		X			
IN-THEATRE FORM		X			
Wound assessment/ review (blinded)			X	X	X
RETURN TO THEATRE FORM			X*		
Wound healing questionnaire CRF				X	X
Health utility questionnaire CRF (Resource Usage)**				X	X+

*Only to be completed if patient is required to return to theatre for any reason.

** Health resource usage will only be collected on those participants in the final phase of the trial.

+ A Microbiology Sub-Study will be conducted during the final phase of the trial, more details will be provided in upcoming amendments.

8.4. Trial Follow-Up Assessments

Participant retention will be maximised by minimising deviation from the usual postoperative patient pathway.

8.4.1. Pre-discharge/ Day 7 Wound Review

At day 7 (assessment window: days 5 to 7), or at discharge (if sooner), a blinded in-person wound review should be performed. The wound will be assessed for an infection according to the CDC SSI criteria.
The assessment will be undertaken by a member of the research team who has been trained in the diagnosis of wound infections and who is blinded to the randomised allocation.
As part of this wound inspection, the Wound Assessment (Day 7) CRF will be completed.

8.4.2. Day 30 Wound Review

At 30 days post-operation (assessment window days 30-37; with day 0 being the day of surgery) a blinded in-person wound review should be performed. The wound will be assessed for an infection according to the CDC SSI criteria.

This assessment will be undertaken ideally on day 30 by a member of the research team who has been trained in the diagnosis of wound infections and who is blinded to the randomised allocation and it may be performed at the hospital where they underwent their primary operation, or at an alternative local research clinic as required. In many cases this may mirror standard postoperative care in patients undergoing abdominal surgery.

At this assessment the Wound Assessment (Day 30) CRF should be completed. The patient will also be asked to complete the Wound Healing Questionnaire (WHQ) at this time-point. The WHQ is a single patient and observer measure for post-discharge SSI assessment. It contains 16 data points, that are easily understood and completed with the support of a healthcare professional (64). It has been developed as part of an NIHR HTA-funded (12/200/04) mixed-methods feasibility study of wound dressing strategies to reduce SSI (65, 66).

Participants will be made aware of the requirement for a 30-day follow-up appointment before informed consent is taken. In exceptional circumstances where a patient is unable or unwilling to attend a follow-up appointment at 30-days, every effort will be made to complete the WHQ by telephone to maximise adherence to follow-up. Whilst the number of patients this will apply to is expected to be minimal, the effect of questionnaire-based follow-up only will be assessed in sensitivity analysis.

8.4.3. Wound assessment

The wound will be assessed by a blinded, experienced, clinical investigator trained for this role who has signed the **ROSSINI 2** Site Signature and Delegation Log. Outcome assessments will be undertaken by members of the research team who were not involved in the operation and thus blinded to the trial arm allocated. We anticipate that this group will include local surgical trainees, research nurses and nurse specialists, all of whom will be specifically trained

and accredited as being capable of diagnosing an SSI, using a pre-existing online training tool (see separate appendix). This system will reduce inter-observer variability and make an inherently subjective endpoint as reliable and reproducible as possible.

To maximise the fidelity of follow-up period between discharge and 30 day review, a patient-reported wound healing questionnaire (WHQ) will be completed at the 30 days follow-up visit in conjunction with the researcher.

8.4.4. Follow-up beyond the Primary Study Window

In patients who have an ongoing wound infection at 30-days postoperatively these patients will continue to have ongoing active follow-up outside the study window every 30 days until resolution. This will require:

- Re-examination of the wound.
- Completion of the EuroQol EQ-5D-5L tool, either in person or over the telephone.
- Completion of a Health Utility Questionnaire

This group of patients will include less than 5% of those with an index SSI event, but will account for over 50% of healthcare utility, cost and impact on quality of life. A protracted follow-up period will allow **ROSSINI 2** to assess the incremental impact of the most 'severe' SSI.

8.5. Participant Withdrawal

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial (or part of) at any time.

Types of withdrawal as defined are:

- The participant would like to withdraw from trial treatment, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis)

- The participant would like to withdraw from trial treatment and does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes)

- The participant would like to withdraw from trial treatment and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source documents and the **ROSSINI 2** trial office informed.

Primary outcome data (SSI rate at 30 days) from participants who have withdrawn from the **ROSSINI 2** study will be derived where possible from routine outpatient follow-up appointments or hospital records where necessary. The impact of this on the study findings will be explored in a sensitivity analysis.

9. ADVERSE EVENT REPORTING

9.1. General Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a participant or a clinical trial subject which does not necessarily have a causal relationship with the device/procedure.

A Serious Adverse Event (SAE) is an untoward occurrence that:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the Investigator

As **ROSSINI 2** is a non - CTIMP, BCTU will not be collecting Suspected Unexpected Serious Adverse Reactions (SUSARs). We will however be collecting Related and Unexpected SAEs.
A **Related and Unexpected Serious Adverse Event (RUSAE)** means a SAE occurring to a research participant which in the opinion of the Chief Investigator was:

- 'Related' that is, it resulted from the administration of any of the research procedures, and
- 'Unexpected' that is, the type of event is not listed in the protocol as an expected occurrence.

Medical and scientific judgement must be exercised in deciding whether an event is serious. These characteristics/ consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

9.2. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care and the requirements of the Health Research Authority

(HRA). Definitions of different types of AEs are listed in the table of abbreviations and definitions. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant this should be documented in the source data with reference to the protocol.

9.2.1. Adverse Events (AE) in ROSSINI 2

AEs are commonly encountered in participants undergoing colorectal, hepatobiliary, upper GI, urological, vascular, or gynaecology operations. As the safety profiles of the interventions used in this trial are well characterised, it is highly unlikely that this trial will reveal any new safety information relating to these interventions. The recording of selected AEs will therefore not affect the safety of participants or the aims of the trial. For this reason, only AEs that may be expected or 'related and unexpected' to the interventions that are experienced during surgery and up to 30 days post-surgery will be reported.

9.2.1.1. Expected Adverse Events (AE) in ROSSINI 2

AEs that may be expected as a result of the surgery, the interventions or control (surgeon's preference) should be reported via the Wound Assessment on Day 7 and Wound Assessment on Day 30 CRFs. These are:
Infection related:

- Pain or tenderness at the incision site
- Localised swelling
- Redness at the incision site
- Heat at the incision site
- Fever

Complication related:

- Granuloma
- Haematoma
- Seroma
- Dehiscence

9.2.2. Serious Adverse Events (SAE) in ROSSINI 2

All events which meet the definition of serious will be collected and recorded in the participant medical notes. Only SAEs that may be expected or 'related and unexpected' to the interventions and are experienced during surgery and up to 30 days post-surgery will be reported.

9.2.2.1. Expected Serious Adverse Events requiring Expedited Reporting in ROSSINI 2

The following SAEs should always be recorded and reported to the BCTU Trials Office as a SAE, on the SAE FORM:

- Skin reactions
- Allergic reactions

- Combustion

9.2.2.2. Expected SAEs requiring standard reporting within ROSSINI 2

Other SAEs that may be expected as a result of the surgery, the interventions or control (surgeon's preference) should be reported via the Wound Assessment on Day 7 and Wound Assessment on Day 30 CRFs. These events will be captured and will be reported as summated SAEs to the DMEC:

- Interventions (either within theatre, radiology department or on the ward) to drain wound infections
- Prolonged hospital stay as a result of wound infections
- Anastomotic leak
- Intra-peritoneal collections (with or without intervention)
- Thrombo-embolic events
- Infections not related to the wound (eg. pneumonia, urinary tract infections)
- Cardiac or central nervous complications
- Paralytic ileus

SSIs, wound infections and complications do not need to be reported on a SAE form, as these data will be captured during routine CRF collection.
Patients may suffer from other complications from their surgery but if these are not related to their wound or the interventions, they do not need to be reported.

9.2.3. Events not requiring reporting

The following events are excluded from reporting to the Trials Office but should be recorded within the participant's notes only:

- SAEs that are related to a pre-existing condition
- SAEs that are related to symptoms or progression of the participant's disease
- Pre-planned hospitalisations.

9.2.4. Monitoring pregnancies for potential Serious Adverse Events

There is not an identified risk of congenital anomalies or birth defects in the offspring of participants as a result of their participation in the trial. As this is the case, pregnancies will not be monitored for any potential SAEs.

9.3. Reporting Period

Details of all AEs and SAEs that are being monitored as defined in section 9.2 will be documented in source data and where applicable, reported from the date of randomisation until the Day 30 Assessment post-surgery. SAEs that are judged to be at least possibly related to the use of any of the interventions must still be reported in an expedited manner irrespective of how long after surgery the event occurs.

9.4. Reporting Procedure – At Site

9.4.1. Adverse Events

During the pilot phase of **ROSSINI 2**, AEs should be recorded via the Wound Assessment on Day 7 and Wound Assessment on Day 30 on paper CRFs.

During the main phase of **ROSSINI 2**, AEs should be recorded via the Wound Assessment on Day 7 and Wound Assessment on Day 30 via the electronic CRFs.

9.4.2. Serious Adverse Events

During the pilot phase of **ROSSINI 2**, SAEs that may be expected or 'related and unexpected' to the interventions and are experienced during surgery and up to 30 days post-surgery, that are **not** routinely collected on the CRFs, should be reported as an SAE on the paper **ROSSINI 2** SAE Form. During the main phase of **ROSSINI 2**, SAEs should be reported via the electronic CRFs.

When completing the SAE form, the Investigator will be asked to define the causality and the severity of the AE. This will be on a five-point scale as described in Table 3.

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

Table 3. Five point scale describing causality of adverse events.

On becoming aware that a participant has experienced an SAE, the Investigator (or delegate) must report the SAE to their own Trust in accordance with local practice and to the **ROSSINI 2** Trial Office at BCTU.

To report an SAE to the Trial Office at BCTU, the Investigator or delegate(s) must complete, date and sign the **ROSSINI 2** SAE form. The completed form should be faxed or emailed to the BCTU trials team using the number listed below as soon as possible and no later than **24 hours** after first becoming aware of the event:

To report an SAE, fax or email the SAE form to:

0121 415 8871 or email to ROSSINI2@trials.bham.ac.uk

On receipt of an SAE form, the **ROSSINI 2** trials team will allocate each SAE a unique reference number and return this via fax or email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number, the site should contact the BCTU trials team within 1 working day. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE form in the ISF.

Where an SAE form has been completed by someone other than the Investigator, the original SAE form will be required to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

9.4.3. Provision of follow-up information

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a Data Clarification Form (DCF), using the SAE reference number provided by the BCTU trials team. Once the SAE has been resolved, all follow-up information has been received and the paperwork is complete, the original SAE form that was completed at site must be returned to the **ROSSINI 2** trials office and a copy kept in the Site File.

9.5. Reporting Procedure – ROSSINI 2 Trials Office

On receipt of a SAE form from the site, the **ROSSINI 2** trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. An email (containing the completed unique reference number) will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE form in the Trial Master File (TMF).

On receipt of an SAE form the CI or delegate will independently review the causality of the SAE. An SAE judged by the CI to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Event (SAE). The causality assessment given by the PI will not be downgraded by the CI. If the CI disagrees with the PI's causality assessment, the opinion of both parties will be documented and where the event requires further reporting, both opinion will be provided with the report.

The CI will also perform an assessment of expectedness on all SAEs received on a SAE form. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

9.6. Reporting to the Research Ethics Committee

9.6.1. Related and Unexpected Serious Adverse Events (RUSAE)

BCTU will report all events categorised as Related and Unexpected SAEs (RUSAE) to the main Research Ethics Committee (REC) and the Research Governance Team (RGT) at the University of Birmingham within 15 days of being informed of the event.

9.6.2. Other safety issues identified during the course of the trial

The main REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial.

9.7. Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to the PI. A copy of any such correspondence should be filed in the site file and TMF.

9.8. Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will assess the safety profile of the trial via summary reports of all related and unexpected SAEs that have occurred in the trial and will review any and all SAEs upon request.

9.9. Reporting to Third Parties

Becton Dickinson UK LTD, 3M United Kingdom PLC and SERB will be notified of any SAEs that occur in participants treated with their product alone or in combination.
These will be forwarded on a regular basis (monthly or quarterly) and sent as a list of events. No patient identifiable information will be given to the company.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Source documents are kept as part of the participants' medical notes (paper or electronic) and will be generated and maintained at site. In addition, for this trial, QoL questionnaires (EQ-5D-5L), Wound healing questionnaires and Health utility questionnaires will be performed; the copies of questionnaires will remain at sites in the patient's records whilst the originals (source data) will be forwarded to the BCTU.

CRFs generated from source will be completed at the time points detailed in Section 10.4.

10.2. Data handling during pilot phase of ROSSINI 2

For the pilot phase of **ROSSINI 2**, CRFs will be completed on paper at each site with the original forwarded to the BCTU upon completion. The copies will be kept at the local site. The trial office will be responsible for uploading the data from hard copies into the electronic CRF. The electronic CRF will be held on a secure database at Birmingham Clinical Trials Unit.

10.3. Data handling during main phase of ROSSINI 2

For the main phase of **ROSSINI 2**, source data will be input onto the secure eCRF directly by staff at sites. Data management will then continue as described in section 10.6.
At no point in the trial, for any given site, will there be simultaneous access to the ROSSINI-2 trial database by both the BCTU and the site.

10.4. Case Report Form (CRF) Completion

CRF Name	Schedule for Submission (To BCTU)
Baseline	At point of consent
Randomisation Form	At the point of randomisation
In-Theatre Form	As soon as possible after day of surgery
Return to Theatre Form	As soon as possible after day of surgery
Wound Assessment (Day 7 or before discharge)	As soon as possible after each follow-up assessment time point
Would Assessment (Day 30)	As soon as possible after each follow-up assessment time point
EQ-5D-5L	As soon as possible after each follow-up assessment time point
SAE	Within 24hrs of research staff at site becoming aware of the event.

Table 4. List of Case Report Forms used within the ROSSINI 2 trial.

Case Report Form (CRF) definitions:

Baseline:

Basic demographic data including age, sex, BMI, comorbidity etc

Randomisation Form:

Contains all details required to randomise a patient

In-Theatre Form:

Theatre data including interventions used, operative details etc

Wound Assessment (Day 7 or before discharge):

First blinded wound review

Wound Assessment (Day 30):

Second blinded wound review including patient-completed questionnaire (WHQ) covering post-discharge period

Return To Theatre Form:

Contains all details including reasons why patient has to return to theatre.

EQ-ED-5L:

Quality of Life Questionnaire

Resource Usage Form – Health resource usage will only be collected on those participants in the final phase of the trial.

Data reported on each CRF will be consistent with the source documents and any discrepancies will be explained. Only delegated staff on the **ROSSINI 2** Site Signature and Delegation Log and those trained in GCP are able to complete the CRFs. CRF completion guidelines will be sent to all sites and will include guidance on:

- CRF completion and corrections
- Date format and partial dates
- Rounding conventions (if applicable)
- Trial-specific interpretation of data fields
- Which forms to complete and when
- What to do in certain scenarios, for example when a subject withdraws from the trial
- Missing/incomplete data
- Completing SAE forms and reporting SAEs
- Protocol and GCP non-compliances

In all cases it remains the responsibility of the site's PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI, on the paper CRF and on the eCRF during the main phase of the trial.

For paper CRFs, the originals will be forwarded to the **ROSSINI 2** Trials Team and the copies filed in the patient's records. For all QoL questionnaires (EQ-5D-5L), Wound healing questionnaires and Health utility questionnaires performed; the copies of questionnaires will remain at sites in the patient's records whilst the originals will be forwarded to the BCTU.

Only CRFs specified in the protocol must be used.

10.5. Participant completed Questionnaires

Participants will be asked to complete a health - related QoL questionnaire (EQ-5D-5L) at Baseline (after consent, before randomisation), Day 7 (or discharge if sooner) and Day 30. Participants will also be asked to complete the WHQ at Day 30 and then every 30 days until the wound has fully healed. These questionnaires can be completed as an inpatient, in clinic or on the ward with the support of the research nurse or trainee surgeon, if necessary.

If a patient have been discharged, and has provided consent, research staff at site may telephone a participant and complete all questionnaires by proxy. Site staff or ROSSINI 2 Trial staff may also post the QoL and WHQ questionnaires to the participants for completion and it be returned to the **ROSSINI 2** Trial Office <insert address>.

10.6. Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific data management plan. Coding and validation will be agreed between the trial's coordinator, statistician and programmer and the trial database will be signed off once the implementation of these has been assured.

Paper CRFs must be completed, signed, dated and the originals should be posted to the **ROSSINI 2** Trial Office. A copy must be kept at the local site. The **ROSSINI 2** trial office will be responsible for uploading the data from original paper CRFs into the electronic CRF. Entries on the paper CRFs should ideally be made in ball point pen, in black ink and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. The **ROSSINI 2** Trial Office will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent DCFs (Data Clarification Forms) requesting missing data or clarification of inconsistencies or discrepancies.

Data reported on each CRF should be consistent with the source document or the discrepancies should be explained. If information is not known, this must be clearly indicated on the CRF. Completed CRFs will be reviewed by the **ROSSINI 2** trial office for completeness and all missing and ambiguous data will be queried using a Data Clarification system in line with the **ROSSINI 2** Data Management Plan and will focus on data required for trial outcome analysis and safety reporting. Data Clarification Forms (DCFs) will be generated on a regular basis by **ROSSINI 2** trial office staff and reported to the site for clarification.

All sections are to be completed. In all cases, it remains the responsibility of the Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate. PIs will be required to sign off on all CRFs.

The electronic CRFs will be held on a database at the University of Birmingham.

Questionnaires completed remotely by participants will be received by BCTU and will be transcribed directly onto the database. Given that these are patient reported outcomes, a data query process cannot be implemented.

Self-evident corrections by the **ROSSINI 2** trial office are permitted. (Found in "Appendix - Self-evident corrections").
CRF formatting may be amended and the versions updated by the **ROSSINI 2** trial office, as appropriate, throughout the duration of the trial. Whilst this may not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt.

10.7. Data Security

The security of the System is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the Global Data Protection Regulations 2018 (GDPR). The University will designate a Data Protection Officer upon registration of the study. The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate storage of non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software and separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).
- Data processing: Statisticians will only have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - An annual IT risk assessment
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

10.8. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years. No documents will be destroyed without prior approval from the Trials Office.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Site Set-up and Initiation

The CI is required to sign a UoB CI agreement to document the expectations of both parties. The UoB CI agreement document must be completed prior to participation. The CI is required to sign a Clinical Trials Task Delegation Log which documents the agreements between the CI and BCTU. In addition all local PIs will be asked to sign the necessary agreements and contracts including a Site Signature and Delegation log between the PI and the CTU and supply a current CV and GCP certificate to BCTU. All members of the site research team are required to sign the **ROSSINI 2** Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation either by a meeting or a teleconference, at which key members of the site research team are required to attend. Key members must have completed GCP training. The Site Initiations at all sites will cover aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Where possible, site teams from across different eligible surgical specialties (e.g. Colorectal, Gastro-esophageal, Gynaecological, Hepatobiliary surgery) will all be invited to this initiation visit to build efficiencies within the site team. Sites will also be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed immediately of any change in the site research team.

Before opening, all sites will receive trial-specific training, both on the logistical and operational aspects of the trial and in the correct use of the various interventions to ensure a standardised and optimal method of use. This will mitigate risk of harm through improper application, whilst being minimal disruptive to broader clinical practice at the site.

11.2. Monitoring

Due to the nature of **ROSSINI 2** there is a need for monitoring to ensure safety of participants, clinician acceptability, adherence to arm allocation, clinician effectiveness of each arm and the credibility of the data. Monitoring will be performed in accordance with the **ROSSINI 2** Monitoring Plan by visiting the trial site(s) ('on-site monitoring') which gives the benefit of access to source documents. Centralised monitoring techniques will also be employed. Findings generated from monitoring will be shared with local R&D departments.

11.2.1. Onsite Monitoring

Onsite Monitoring will be carried out as required following trial specific risk assessment and as documented in the monitoring plan. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required the Trials team will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the **ROSSINI 2** trial staff access to source documents as requested. The monitoring will be conducted by members of the **ROSSINI 2** trials team.

11.2.2. Central Monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

11.3. Audit and Inspection

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

11.4. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, Trial Steering Committee, and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC. A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC.

12. END OF TRIAL DEFINITION

The end of trial will be twelve months after the last data capture (date of last data capture will be approximately 30 days post-surgery). This will allow sufficient time for the completion

of protocol procedures, data collection and data input. The Trials Office will notify the main REC and RGT that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.
Where the trial has terminated early, the Trials Office will inform the REC within 15 days of the end of trial.

A copy of the end of trial notification as well as the summary report will also be sent to the University of Birmingham Research Governance Team at the time these will be sent to the REC.

13. STATISTICAL CONSIDERATIONS

13.1. Sample Size

13.1.1. Justification of sample size

The justification for the sample size is based on evidence from high-quality prospective registries, international audits and randomised controlled trials using the CDC definition of SSI.

Author	Year	Type	Type of surgery	n=	SSI rate (%)
Smith *et al.*	*2004*	Prospective registry	Colorectal	176	26.0
Blumetti *et al.*	*2007*	Prospective registry	Colorectal	428	25.0
Howard et al.	*2010*	Prospective registry	Colorectal	122	25.3
Daneman *et al.*	*2010*	National surveillance programme	Colorectal	25086	22.2
Serra-Aracil *et al.*	*2011*	Prospective registry	Colorectal	611	24.9
VINCat	*2014*	National surveillance programme	Colorectal	13661	20.7
			Total	**40084**	**24.0**

Table 5. Summary of SSI rates from high-quality prospective registries

In an unweighted pooled analysis of high-quality prospective registries,n=40084 (Table 5) the SSI rate was 24.0%. In the GlobalSurg 2 international multicentre prospective audit of SSI across 76 countries, patient-level outcomes were recorded after 15830 abdominal operations. The overall SSI rate varied significantly across HDI (human development index) tertiles but when limited to High HDI countries such as the UK (n=8470), the overall SSI rate after open abdominal surgery was 18%.

Author	Year	Intervention assessed in RCT	Type of surgery	n=	Control arm SSI rate (%)
Suzuki et al.	2003	Nasal decontamination	Digestive	395	22.0
Itani et al.	2006	Prophylactic antibiotics	Colorectal	1002	26.2
Meyhoff et al.	2009	High concentration oxygen	Abdominal	1386	20.1
Anthony et al.	2011	Bundle of interventions	Colorectal	211	24.0
Pinkney et al.	2013	Wound edge protector	Abdominal	760	25.3
Tanaka et al.	2015	Wound lavage	Liver	193	21.9
			Total	**3947**	**23.3**

Table 6. Summary of SSI rates from control arm of high-quality RCTs

An unweighted pooled analysis of high quality RCTs in which SSI was the primary endpoint (Table 6) and is thus formally assessed in a protocolised fashion with in-person post-discharge review, provided a mean SSI rate of 23.3% (n=3947).

For **ROSSINI 2** a conservative control group SSI rate of 15% was selected to account for the increasing use of minimal access operative techniques across the study population.

13.1.2. Cohort enrichment

We recognise that certain patient groups eligible to enter the trial (eg clean surgery) will carry a lower baseline SSI rate, and if these groups are over-represented, there is the potential for the trial to become underpowered. This issue must be counterbalanced with the deliberately pragmatic nature of the trial and the requirement to produce generalizable results that are relevant and can be applied to real-world clinical practice.

'Cohort enrichment' will provide confidence that **ROSSINI 2** will produce useful and robust results. We propose to monitor (through the TSC) two groups of patients to ensure that pre-set proportions are met throughout the trial, giving the DMC the ability to modify these proportions if needed, according to the control arm SSI rate, which will be made available to them by the independent DMC at each of the pre-planned interim analysis points:

- *Emergency operations:* it is known that emergency abdominal surgery carries a significantly higher SSI rate, both due to the pathological indications for emergency surgery causing increased levels of contamination and the worse physiological status of the patients themselves. We will stipulate that a minimum of 20% of the overall cohort entering the trial should undergo emergency surgery. It is a challenge to recruit patients within the acute setting, but our research network of trainees has previously demonstrated its ability to access and recruit such patients; in our ROSSINI 1 trial the proportion of patients undergoing emergency abdominal surgery successfully recruited into the trial was 22%.
- *Laparoscopic (minimal access) operations:* the trial needs to include minimally invasive surgery to ensure it is relevant to modern abdominal surgical practice. The current proportion of abdominal surgery performed laparoscopically varies depending on the speciality, but current UK data suggests 40% of colorectal resections (70), 25% of liver resections (71) and 25% of upper gastrointestinal resections (72) are performed laparoscopically. We have included operations starting laparoscopically, providing there will be a specimen extraction site of at least 5cm, as is the case for most resectional surgery. This minimum wound size stipulation is necessary both to allow application of all interventions under investigation, some of which are inserted into the open wound, and also to maintain the baseline event rate as above by excluding more minor operations such as laparoscopic cholecystectomy or appendicectomy. Reported SSI rates after major resectional laparoscopic operations eligible for the trial are reported 30-45% lower than the corresponding open surgery operations (29, 30, 73-75). For these reasons we will stipulate that a minimum of 50% of the overall cohort should be undergoing open surgery.

13.1.3. Sample size calculation

The sample size is based on an assumption that the SSI rate in the control arm will be 15%. For all research arms, we are targeting a reduction in this rate to 10%, with a loss to follow-up of 4% of patients. The trial is planned in 3 stages, two interim and on final. At each interim stage we have allowed for the possibility that two research arms will not randomise any further patients; from 7 to 5 research arms at the end of the first stage and 5 to 3 research arms at the end of the second stage. The first stage analysis once approximately 2350 patients shave joined the trial and the second stage analysis is planned when approximately 4630 patients have been recruited. Given this design, it is anticipated that approximately 6610 patients will be entered into the trial.

13.1.4. Projected recruitment

The knowledge gained from running ROSSINI 1 has been invaluable in our recruitment predictions. We know that 50 to 160 eligible operations will be undertaken each month at each site, with all specialities included. It is likely that the trial will recruit primarily from general surgery, which still leaves 30 to 100 operations per month. In ROSSINI 1, one site randomised 5 patients in a single day. Our recruitment target of 4 patients per month per site represents a conservative estimate.

Table 7. Overall sample size and design assumptions

Overall sample size	Approximately 6610 patients across all arms and stages
Total number of stages	3 stages (excluding pilot stage)
Total number of arms	8 arms at the beginning (1 control, 7 research arms) 6 arms after Stage 1 analysis (1 control, 5 research) 4 arms after Stage 2 (1 control, 3 research)
Allocation ratio	2:1 = Control : Research
Primary Outcome Measure	Proportion of patietns reporting Surgical Site Infections up to 30 days after surgery. This will be used as both intermediate and final outcome measure in stages 2, 3 and 4.
Control arm SSI rate at 20 days after surgery	15%
Targeted Research arm SSI rate at 30 days after surgery	10% (33.3% relative reduction)
Lost to follow-up or patients without data	4%

13.1.5. Allocation Ratio

During Stage 1 the allocation ratio is A : B : C : D : E : F : G : H = 2 : 1 : 1 : 1 : 1 : 1 : 1 : 1. Arm A is a comparator for all arms, so each research arm will be compared with the control arm A individually (pairwise comparison). When arms are dropped at Stage 2 and 3 analyses, allocation ratio will remain 2:1 for control:research. We propose to randomise more patients to the control arm than research arms to maximise the power for each pairwise comparison. It is anticipated that the pilot phase will run for the first 6 months and it is expected that an average of 4 patients/month will be achieved by each site. Sites will open during the main phase at a rate of 4 per month; each open site recruiting an average of 4 patients per month. This target is entirely achievable based on our experience with the ROSSINI 1 trial.

Significance level, power, family-wise error rate: No formal comparison between research and control arms will be performed at the end of the pilot stage. The one-sided significance level and power, for stages 2, 3 and 4 are 0.40, 0.14, 0.005 and 94%, 94%, 91% respectively (Table 8). These values are used to ensure that there is an overall family wise error rate of 0.025 one-sided and overall (pairwise) power of 85%. The family wise error is defined as the probability of rejecting at least one true null hypothesis at the end of the trial. Statistical literature (59-61) for MAMS trial designs advises using first stage significance level between 0.2 and 0.5 one-sided. This is a similar approach to the significance levels used for phase II trials. Loss to follow-up: It is assumed that 4% of patients will be lost to follow-up or the primary outcome evaluation will be missing, e.g. surgery not done. This is based on the data from ROSSINI 1 trial (25), where the primary outcome measure was missing for 25/760, 3.3% patients (14/760 lost to follow-up, and 11/760 laparotomy not done). We anticipate that

the time to decision about continuing or stopping recruitment to the research arms will be approximately 4 months: For the analyses at the stages 2 and 3, once the target number of patients is recruited, it is expected that around 4 months will pass 16/31/123 13 until the decision time regarding stopping and/or continuing research arm(s). This is to allow for 30 day FU, CRFs to be completed and posted to the coordinating Clinical Trials Unit, data to be entered, interim analysis to be performed, Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) meetings to be held. The DMC will make a recommendation and TSC will make the final decision regarding stopping and/or continuing recruitment to research arms. This decision will take into account both the efficacy, adherence to the treatment and any other relevant factors.

Table 8. Sample Size Details

Stage	Cumulative sample size*	Patients recruited in all active arms	Control/ Research arm patients for analysis	Cumulative time from randomisation to analysis completion	Number of active arms	Targets for 1-sided significance level [Power]	Pairwise 1-sided significance level [FWER]	Pairwise power
1	Pilot	No sample size target	No sample size target	6 months	8	N/A	N/A	N/A
2	2357	2357	402/201	20 months	8	0.40 [94%]	0.004 [0.0254]	85%
3	4632	4108	854/427	29 months	6	0.14 [94%]		
4	Approx. 6610	4915+	1887/944	41 month**	4	0.005 [91%]		

* across all arms. This includes patient who will be recruited by the time of each stage analyses completion
\+ note that this excludes arms dropped at stages 2 and 3, and includes patients recruited in stage 3
** recruitment will be completed around 38 months from the start of trial recruitment

Pilot sample size: It is planned for pilot stage to last 6 months. Formal sample size calculation is not applicable for the pilot stage. Stages 2, 3 and 4 sample size: it is anticipated approximately 402, 854, and 1887 control arm patients will be included in Stage 2, 3 and 4 analyses respectively. Based on the recruitment rate assumption, it is expected that by the time of decision regarding arms in Stage 2, 3 and 4 analyses, 523, 1173 and 1966 control arms will be recruited due to the (a) 4 months' time between the randomisation of the last patient needed for the analysis and time of decision – see above "time to decision" (b) patients who were lost to follow-up. At the end of the trial it is anticipated that approximately 6610 patients will be randomised across all arms. This includes patients from arms which will cease further randomisations at Stages 2 and 3, and arms which will continue until the end of the trial. Recruitment and trial duration: Based on the recruitment assumption, it is expected that recruitment will be completed around 3.1 years from the start of trial recruitment and final results known at 41 months (which excludes the 6 months trial set-up phase). Design characteristics: This design achieves one-sided family-wise error rate of 0.0253, using a one-sided significance level of 0.004 and power of 85% for each pairwise comparison. Sample size was calculated using Stata version 14.2 commands –nstagebinopt- and -nstagebin-.

13.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. The primary comparison groups will be composed of those randomised to the trial interventions either alone or in combination versus those in the control arm. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation. For all major outcome measures, summary statistics and differences between groups, e.g. relative risks and absolutely differences will be presented, with 95% confidence intervals and p-values also given. Analysis of the primary outcomes will be adjusted for the minimisation variables listed in section 6.2 where possible. We are assessing each research arm as 'independent research arms' because we think there may be important interactions between the components of research arms carrying multiple interventions. An adjustment for multiple comparisons has already been made by increasing the proportion of patients in the control arm, and selecting a 0.025 FWER.

Each end-of-stage analysis will be carried out when the required number of patients have contributed data to the primary outcome analysis (see section 13.1.2). Each research arm will be compared to the control arm only. After each analysis, the DMC will review confidential data and will make a recommendation to the Trial Steering Committee, who will make the final decision about continuing and/or stopping recruitment to the research arms. The comparison between the arms will be evaluated with the absolute difference in proportion of patients reporting Surgical Site Infection (SSI) at 30 days (difference: control arm – research arm). A binomial test will be applied. The percentage of patients who have no data on the primary outcome measure (for example because they were lost to follow-up, or were randomised but did not have surgery) will be monitored closely and is accounted for in the sample size calculation.

13.2.1. Primary Outcome Measure

The primary outcome measure of the trial is the presence/absence of surgical site infection (SSI) within 30 days of randomisation. This outcome is a binary outcome (i.e. yes/no). The number and percentage of participants experiencing SSI within 30 days of randomisation will be reported for each research group and the control group. Absolute difference and 95% confidence interval will be estimated from a log-binomial model in order to take into account the minimisation variables listed in section 6.2. The p-value from the associated test statistic will be produced and used to determine statistical significance.

13.2.2. Secondary Outcome Measures

The secondary outcomes for the trial include continuous, categorical and time-to-event data items.

Time to Event Outcomes (e.g. length of hospital stay, mortality)

Time to event outcomes will be compared between treatment groups using standard survival analysis methods. Kaplan-Meier survival curves will be constructed for visual presentation of

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

Categorical Outcomes (e.g. SSI at discharge)

For binary secondary outcomes, the number and percentage of participants reporting each outcome will be reported by treatment group. An adjusted relative risk and 95% confidence interval will be estimated from a log-binomial regression model. The p-value from the associated chi-squared test will be produced and used to determine statistical significance.

Continuous Outcomes (EQ-5D-5L)

Continuous outcomes will be reported using means and standard deviations. The EQ-5D-5L will be compared between treatment groups with adjusted mean differences and 95% confidence intervals estimated using linear regression models. Change in EQ-5D-5L score from baseline may also be modelled.

13.2.3. Exploratory Interaction Analysis

Interaction analyses will be limited to the same variables used in the minimisation algorithm (see section 6.2). Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimate within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

13.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal (less than 4%). Participants with missing primary outcome data (withdrawn from the study, did not undergo surgery or did not attend a follow-up appointment) will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken using modern multiple imputation techniques to assess the possible impact of the risk.

13.3. Planned Interim Analysis

Internal pilot study at 10 sites; staggered opening; total approx. 150 patients randomised followed by Stage 1 STOP/GO interim analysis of adherence to arm allocation and feasibility.

The first formal interim analysis at approximately 2357 patients will include efficacy data to be considered, alongside other important aspects such as adherence and acceptability to enable the DMC to determine which arms to recommend being dropped. At each interim analysis stage it is anticipated that at least two arms will be dropped. These earlier assessments of adherence and feasibility outlined above have been added to the flow chart.

We have 70 sites signed up to join the trial and the surgeons have stated that they are currently in clinical equipoise relating to the interventions under study. Actual uptake and compliance to randomised allocation will be formally assessed at the end of the feasibility study, and arms where clinical equipoise has not been demonstrated, as witnessed by the behaviour of surgeons within the trial, will be adjusted or dropped. The unique MAMS design

of the will also allow us to continue this monitoring process throughout the trial; at each pre-specified interim analysis arms will be chosen for dropping not only on based on their efficacy signal but also on other aspect including compliance, acceptability and cross-over rates. There is the potential for 'gravitation towards the mean' in any trial involving a complex intervention where the local investigator cannot be blinded to the measures used in an individual patient. We think this potential for a surgeon to change their behaviour based on their experiences within the trial is unlikely because the interventions under study are binary (they are either used or they are not), limiting the opportunities for changes in practice within the trial.

13.4. Health economic analysis

Economic evaluation will be carried out to determine the costs and benefits of the compared interventions, with a view to establishing the practice that represents best use of NHS resources. In line with recommendations, the base case analysis will be conducted from the perspective of the NHS and personal social services. Additional analysis will adopt a wider, societal perspective. Results will be presented in terms of cost per additional quality-adjusted life year (QALY) gained. Health economic analysis will be started following the second interim analysis to provide assessment of the most effective three study arms.

13.4.1. Resource use and costs

Information on use of health care resources will be collected alongside the proposed trial through CRFs and patient questionnaires. Relevant data will include: i) costs associated with the purchase and use of the assessed in-theatre interventions under assessment ii) costs associated with the use of postoperative care provided in response to surgical wound infections in the hospital setting (e.g. inpatient stay, outpatient appointments, additional procedures related to wound infection, use of antibiotics) iii) costs due to use of primary care services (GP consultations, appointments with nurses, antibiotics and painkillers provided in the community) and, iv) private (patient) costs and productivity loss related to wound healing. Use of health care resources will be weighted by unit cost values taken from up-to-date national sources and tariffs, including the Unit Cost of Health and Social Care report (70), the British National Formulary and the NHS Reference Cost Schedules.

13.4.2. Outcomes

The main measure of benefit in the economic evaluation will be the quality-adjusted life year (QALY), an outcome that combines expected survival and QoL. QoL will be obtained through patients' responses to the 5- level European Quality of life (EQ-5D-5L)(73) instrument at baseline, 7 days and 30-days post-operation. Each patient's health status descriptions obtained from the EQ-5D-5L will be translated into a single, preference-based (utility) index using a UK specific value set (74). QALYs will be calculated as the area under the curve connecting utility scores reported at the above follow-up points.

13.4.3. Analysis

Given the nature and time frame of the clinical question, relevant costs and outcomes are expected to be largely captured within the study follow-up period. Thus, the main analysis will

be carried out on the basis of patient-level data obtained within the study follow-up. Data will be analysed on an 'intention to treat' basis. Missing data will be accounted for by using appropriate techniques, depending on the extent and type of missing itemsn (75). As the distribution of cost is usually skewed by the existence of patients with very high costs, the calculated mean per patient cost will be given alongside confidence intervals obtained through non-parametric bootstrap methods (76). Incremental analysis will be undertaken to calculate the difference in costs and the difference in outcomes (QALYs) associated with each of the interventions. Results will be presented in the form of incremental cost-effectiveness ratios (ICER), reflecting the extra cost for an additional unit of outcome. To account for the inherent uncertainty due to sampling variation, the joint distribution of differences in cost and outcomes (QALYs) will be derived by carrying out a large number of non-parametric bootstrap simulations (77). The simulated cost and outcome pairs will be depicted on a cost-effectiveness plane and will be plotted as cost-effectiveness acceptability curves (CEACs) (78). CEACs will show the probability of each intervention being cost-effective across a range of possible values of willingness to pay for an additional QALY.

13.5. Planned Final Analyses

The primary analysis for the study will occur once all participants have completed the 30-day assessment and corresponding outcome data has been entered onto the study database and validated as being ready for analysis.

14. TRIAL ORGANISATIONAL STRUCTURE

The Chief Investigator will have overall responsibility for the study. The co-applicants will form the Trial Management Group (TMG) and will meet at least quarterly to discuss and coordinate the project. The project involves close interaction between two established CTUs. The MRC CTU are experts in MAMS trial design and analysis. As well as ongoing input into the design and conduct of the study, they will oversee the statistical team at BCTU in undertaking the data analysis, thereby disseminating specialist knowledge and further enhancing long-lasting benefits from this collaboration going into future projects. The coordinating centre at the University of Birmingham will employ study-specific trials staff to manage the study for the project duration. The trial coordinator will undertake all day-to-day conduct of the trial with oversight provided by the surgery trials team leader. Given the size and complexity of the study, a trial administrator and two data managers will also be appointed to assist in the management and data collection of the trial. In addition to the TMG meetings, the CI and the BCTU trial staff will meet on a monthly basis for ongoing and continual review of study. A Trial Steering Committee will be formed and chaired by an independent chair and will also comprise a patient representative, the Chief Investigator, the trial statistician, an independent surgeon and a clinical trialist. It will meet at the start of the trial, then annually thereafter if the study is proceeding well. The Independent Data Monitoring Committee will consist of an independent statistician and independent clinicians. Its meetings will mirror those of the Trial Steering Committee, and will usually occur 2-4 weeks prior to the Trial Steering Committee meeting. Patients will be at the centre of our project throughout, and their input, both via the named patient co-applicants will be contemporaneously inputted into the management processes as the study progresses.

14.1. Sponsor

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

14.2. Coordinating Centre

The **ROSSINI 2** Trial Office is based at the University of Birmingham Clinical Trials Unit (BCTU).

14.3. Trial Management Group

The Trial Management Group (TMG) is responsible for the day to day management of the trial. Membership of the TMG is listed at the front of the protocol. The role of the TMG is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

14.4. Trial Steering Committee

A single TSC will be created for the ROSSINI-2 Trial and meet via teleconference or face-to-face on approximately a 6-monthly basis or at the request of the DMC to coincide with the timing of the interim analyses.
Membership and duties/responsibilities are outlined in the TSC Charter. The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial, including the practical aspects of the study. Membership of the TSC is listed at the front of the protocol. The TSC will monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy.

14.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants.
The DMC will operate in accordance with a trial specific **ROSSINI 2** Trial Specific charter based upon the template created by the Damocles Group. The DMC will meet at the following interim analysis time points unless there is a specific reason (e.g. safety phase) to amend the schedule:

- First analysis at 120 patients
- Second analysis at 2357 patients
- Third analysis at 4632 patients
- Final analysis at approximately 6610 patients

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC who will convey the findings of the DMC to the TMG and/or the, REC or funders if required. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial will stop early if the interim analyses showed differences between interventions that were deemed to be convincing to the clinical community.

15. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the current data protection requirements in the UK), the EU Clinical Trials directive, Medical devices Regulations and amendment Regulations, and the Guidelines for Good Clinical Practice (GCP).
The protocol will be submitted to and approved by the main REC prior to circulation and the start of the trial. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File, and an annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended.

Before any participants are enrolled into the trial, the PI at each site is required to obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the BCTU trials team.

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

16. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulations 2018 (GDPR).

Participants will always be identified using only their unique trial identification number on the CRF and correspondence between the Trials Office and the participating site. Participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer. Representatives of the Birmingham Clinical Trials Office and Sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

17. FINANCIAL AND OTHER COMPETING INTERESTS

ROSSINI 2 is an investigator-initiated and investigator-led trial funded by the NIHR Health Technology Assessment Programme. All three interventions, including training are provided free-of-charge by BD Infection Prevention (Skin Prep), 3M Infection Prevention (Drapes) and SERB (Sponges).
The trial design, data collection, analyses and interpretation of the findings remain under control of the TMG. No competing interests are declared. The trial data will be owned by the TMG.

18. INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants. With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

19. SUB-STUDIES

19.1. Microbiology sub-study

Whilst we are not using microbiological parameters to diagnose SSI alone, it is prudent to consider that the mechanism of action of all of the interventions under assessment could be influenced by the local concentrations of all, or certain subtypes of pathogenic organisms present within the wound. As such, there are two sub-studies we wish to undertake that may provide confirmatory evidence of our clinical efficacy findings:

1. Patients diagnosed with a SSI after an operation will usually have a wound swab taken by their clinician as part of standard practice, either in hospital or in the community. As such, for patients in whom our routine follow-up tools identify a culture result, we will request that the site forward any pus swab laboratory results listing the organisms and sensitivities identified. This will allow us to identify if certain interventions or combinations of interventions are more effective at reducing certain causative organisms of SSI. It may allow future tailoring of combinations of interventions to try to target all relevant types of pathogenic organisms causing SSI.

2. In 20 random patients in each arm (160 patients total), intraoperative swabs will be taken in theatre at two time points: (1) from the skin/fat of the wound at the end of the intra-abdominal component; (2) then from the skin surface after closure. This will allow assessment of which organisms are present in the wound at the end of the operation depending on which intervention(s) are used.

20. PUBLICATIONS AND OUTPUTS

20.1. Authorship policy

Results and analyses of this trial data will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Chief Investigator and authorship will follow the National Research Collaborative model for publication (76). All investigators will be listed as collaborating authors under a single corporate author group; "**ROSSINI 2** Study Group; West Midlands Research Collaborative". The writing group, trial management group, trial steering group, data monitoring committee, site principal investigators and associate principal investigators, and site co-investigators will be grouped in order to outline their specific level of contribution. Recruitment and randomisation of at least ten patients into the study will qualify an investigator for co-authorship status.

One principal investigator and at least one associate principal investigator per surgical specialty open will be permitted at each site. The first site principal investigator to register will hold overall responsibility for the site study conduct, and will be responsible for submitting a final authorship list from each site. At least on associate principal investigator per site will be permitted. An associate principal investigator must be in a Joint Committee on Surgical Training recognised surgical training scheme, or of equivalent grade (77). The associate principal investigator will support trial approvals, site set-up, within team communication, recruitment, co-ordination of other study team members and support Birmingham Clinical Trials Unit (BCTU) to ensure that all members of the study team have completed mandatory training, and signed the delegate log.

20.2. Publications and impact

This complex study will provide high-level evidence on the clinical efficacy and cost-effectiveness of several interventions used to try and reduce SSI. The multi-arm, multi-stage nature of the trial means that outcomes information will become available at multiple time points throughout the study course. As such, planning a publication schedule is difficult and

the TMG will likely chose to release major clinical effectively results at more than one juncture in addition to at completion of the trial. The timings of these reports will be carefully considered to not negatively affect the trial whilst ensuring that ineffective interventions are dropped from the general surgical armamentarium as soon as possible to help save money for the NHS.

In addition to the above, we will publish the full trial protocol including statistical analysis plan in accordance with SPIRIT guidelines within one year of opening recruitment (78). This will both increase awareness and participation in the study and ensure standardised and homogenous data capture and handling throughout the research. The internal pilot study will be published, reporting feasibility and acceptability outcomes and lessons learnt in the early phase of the trial within two years of opening recruitment. No primary outcome data will be reported. As well publications relating to the primary outcomes of the trial, there is also likely to be ancillary outputs and publications relating to the microbiological, health economic and methodological lessons learnt from this ground-breaking trial, both during the trial and following trial completion.

We will aim for several high impact factor peer-reviewed publications from this project, including the Lancet, Lancet Infectious Disease, British Medical Journal and Annals of Surgery. In addition:

- Reports and presentations will be prepared for the funders, ethics committee, local NHS Trusts and in addition a lay summary will be prepared for regional and national patient groups.
- We will also work with our patient representatives to produce information leaflets for routine use in NHS centres.
- A report will be sent to the WHO patient safety panel for their consideration in the derivation of future SSI prevention and reduction guidelines.
- National and European guidelines: our trial management group contains members of several national and international groups and are thus in a position to directly influence future specialty guidelines on this topic.
- NICE guidance: we will work with NICE to produce best guidance information for commissioners and clinicians.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of Birmingham Clinical Trials Unit with funding from a Health Technology Assessment grant from the National Institute of Health Research. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site. If centres in Northern Europe open and recruit for **ROSSINI 2**, individual countries will be allowed to publish their efficacy results, however the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the TMG decides otherwise. Participants will be provided with the study results after the Final Study Report had been compiled and/or after the paper describing the primary outcome had been published.

20.3. Presentations

We will present at national and international meetings, including the Association of Surgeons of Great Britain and Ireland, the Association of Coloproctology of Great Britain and Ireland, the European Society of Coloproctology, the American College of Surgeons Annual Clinical Congress and the Society of Clinical Trials. This will capture an extremely large audience of clinicians nationwide and worldwide. The major UK conferences will be approached to organise yearly sessions to highlight progress of the study and then a plenary session to report results.

21. REFERENCE LIST

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22. APPENDICES