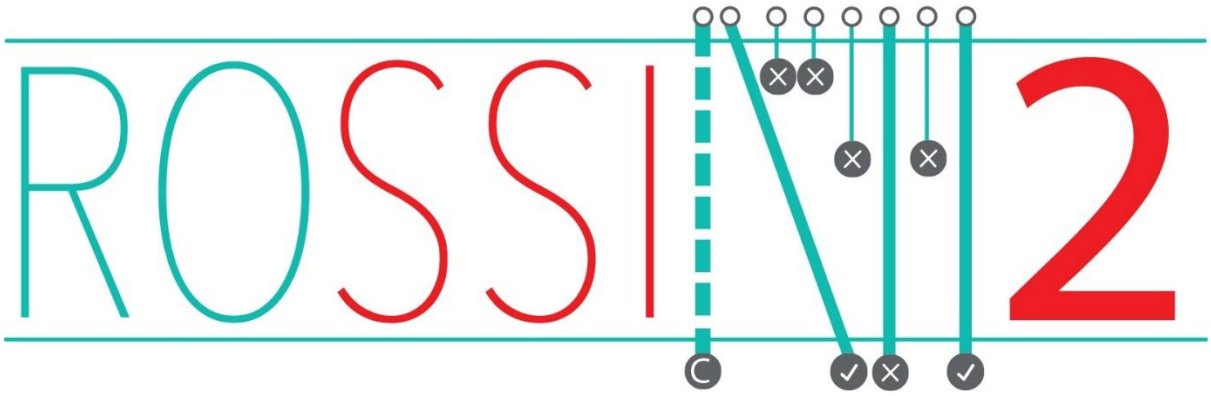


TRIAL PROTOCOL

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 several in-theatre interventions, used 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 the SPIRIT guidelines (2013).

Version Number:	**4.0**
Version Date:	**24th February 2023**

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit

Protocol Development

FUNDING AND SUPPORT IN KIND	
Funder	**Financial and non-financial support given:**
National Institute of Health Research University of Southampton Alpha House Enterprise Road Southampton SO16 7NS	Financial; investigator led grant
Funding scheme	NIHR Health Technology Assessment (HTA) Programme
Funder's reference number	16/31/123
The Funder of this trial has no role in the trial design, data collection, data analysis, data interpretation or in the writing of the final report. This project is funded by the NIHR HTA Programme. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care	

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 sponge [SPONGE]

Protocol Sign Off

Chief Investigator (CI) Signature Page

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

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 trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Name:	**ROSSINI 2**
Protocol Version Number:	Version 4.0
Protocol Version Date:	24th February 2023
CI Name:	Professor Thomas Pinkney
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 trial will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research, the Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) Signature Page

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

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

Trial Name:	**ROSSINI 2**
Protocol Version Number:	Version 4.0
Protocol Version Date:	24th February 2023
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	Protocol Date	Protocol version number	Summary of amendment
SA_01	18th July 2020	V2.0	- Addition of COVID-19 sections throughout to provide information on risks (none), further secondary objectives and changes to patient pathway - Addition/ Change of Staff - Minor word changes for clarification purposes - Clarification regarding secondary objectives - Update of intervention guidelines - Modification to inclusion criteria - Modifications to exclusion criteria to exclude pregnant, breastfeeding patients and operations where the wound is not anticipated to be closed primarily - Additional section provided for clarity on eligibility - Clarification to patient pathway throughout - Additional section provide regarding bovine collagen within the SPONGE - Clarification provided regarding follow up beyond the primary trial window - Clarification regarding withdrawal from the trial - Clarification regarding Safety Reporting - Clarification regarding Data handling - Additional section relating to Protocol Non-Compliances - Clarification regarding the NIHRs Associate PI Scheme
SA_02	12th July 2022	V3.0	- Stage 2 Summary of Completion (First Interim Analysis) provided - Addition of remote Consent - Implementation of Patient Reminder Cards - Clarification regarding the conduct of Wound Assessments - Update to Trial Schedule of Assessments - Further clarification provided regarding follow up beyond the primary outcome assessment window - Minor word changes for clarification purposes
NSA_22	24th February 2023	V4.0	- Stage 3 Summary of Completion (Second Interim Analysis) provided - Addition/ Changes to the Research Team - Minor word changes for clarification purposes

Administrative Information

SPONSOR	
University of Birmingham	
Research Governance Team University of Birmingham Birmingham B15 2TT	✉ researchgovernance@contacts.bham.ac.uk ☎ 0121 414 7618

CHIEF INVESTIGATOR	
Professor Thomas Pinkney	George Drexler & Royal College of Surgeons Chair of Surgical Trials, and Honorary Consultant Colorectal Surgeon
University Hospitals Birmingham NHS Foundation Trust	☎ 0121 415 9100 ✉ Thomas.Pinkney@uhb.nhs.uk

INDEPENDENT DATA MONITORING AND ETHICS COMMITTEE	
Professor Michael Campbell (CHAIR) Emeritus Professor of Medical Statistics University of Sheffield	Professor Nigel Hall Associate Professor of Paediatric Surgery University of Southampton
Professor Ian Chetter Professor of Surgery and Director of Research University of Hull	

TRIAL STEERING COMMITTEE	
Professor David Beard (CHAIR) Professor of Musculoskeletal Sciences University of Oxford	Professor Jane Nixon Professor of Tissue Viability and Clinical Trials Research University of Leeds
Associate Professor Natalie Blencowe Associate Professor in Surgery and MRC Clinician Scientist University of Bristol	Miss Sue Blackwell (PPI)

TRIAL MANAGEMENT GROUP	
TRIAL MANAGEMENT AND METHODOLOGY	
Professor Thomas Pinkney George Drexler & Royal College of Surgeons Chair of Surgical Trials University of Birmingham	Professor Dion Morton Barling Professor of Surgery University of Birmingham
Professor Max Parmar Professor of Medical Statistics and Epidemiology University College London	Dr Babak Choodari-Oskooei Medical Statistician University College London
Dr Kelly Handley Senior Medical Statistician University of Birmingham Clinical Trials Unit	Dr Laura Magill Senior Lecturer in Clinical Trials University of Birmingham Clinical Trials Unit
Mrs Manjinder Kaur Trials Management Team Leader University of Birmingham Clinical Trials Unit	Miss Kayley King Senior Trial Manager University of Birmingham Clinical Trials Unit
SURGERY	
Mr Aneel Bhangu University of Birmingham	Miss Elizabeth Li University of Birmingham
Mr Richard Wilkin University of Birmingham	Mr Neeraj Lal University of Birmingham
Mr Pritam Singh University Hospitals Birmingham	Mrs Georgia Layton University of Birmingham
Mr Dmitri Nepogodiev University of Birmingham	Mr James Glasbey University of Birmingham
Miss Arooj Syed University Hospitals Birmingham NHS Foundation Trust	Miss Fatima Mansour West Midlands Research Collaborative
Miss Nichola Manu University of Warwick	

HEALTH ECONOMICS	
Dr Lazarus Andronis Associate Professor of Health Economics University of Warwick	

MICROBIOLOGY	
Dr Martin Gill Microbiologist University Hospitals Birmingham	

PATIENT REPRESENTATIVE	
Mr Leon Pollock	Mr Pete Wheatstone
Dr Samantha Cole	

TRIAL OFFICE CONTACT DETAILS	
Kayley King	Senior Trial Manager
Megan Garbett	Senior Data Manager
Aileen Ong	Data Manager
Birmingham Clinical Trials Unit Institute of Applied Health Research Public Health Building University of Birmingham Birmingham B15 2TT	☎ 0121 415 8840 🖷 0121 415 8871 ✉ rossini2@trials.bham.ac.uk
Randomisation Service	☎ 0800 2802 307 https://w3.abdn.ac.uk/hsru/ROSSINI2
Trial website & Social Media	www.birmingham.ac.uk/rossini2 @ROSSINI2Trial

REFERENCE NUMBERS	
Sponsor number	RG_18-186
ISRCTN reference number	78305317
Clinicaltrials.gov reference number	NCT03838575
IRAS reference number	247285
CPMS number	39722

ABBREVIATIONS

ABBREVIATION	TERM
ABPI	The Association of the British Pharmaceutical Industry
AMR	Antimicrobial Resistant
API	Associate Principal Investigator
APR	Annual Progress Report
BCTU	Birmingham Clinical Trials Unit
CCG	Clinical Commissioning Groups
CDC	Centers for Disease Control and Prevention
CEAC	Cost Effectiveness Acceptability Curve
CHaRT	The Centre for Healthcare Randomised Trials
CHG	Chlorhexidine Gluconate
CI	Chief Investigator
CPMS	Central Portfolio Management System
CQUIN	Commissioning for Quality and Innovation
CRF	Case Report Form
CTU	Clinical Trials Unit
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
GCP	Good Clinical Practice
GP	General Practitioner
GRIPP	Guidance for Reporting Involvement of Patient and the Public
HRA	Health Research Authority
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
ISF	Investigator Site File
MAMS	Multi-arm, Multi-stage

MRC CTU	Medical Research Council Clinical Trials Unit
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PI	Principal Investigator
PIS	Patient Information Sheet
PNC	Protocol Non-Compliance
POMR	Perioperative Mortality Rate (POMR)
PPI	Patient and Public Involvement
PRC	Patient Reminder Card(s)
QALY	Quality-adjusted life year
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	Research Governance Team
RUQ	Research Use Questionnaire
SAP	Statistically Analysis Plan
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.
REDCap		REDCap is a secure web platform for building and managing online databases and surveys, used within ROSSINI 2.
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 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. Only applicable in Stage 1 (Pilot) and Stage 2 (up to interim analysis one).
SPONGE		Gentamicin-impregnated sponge provided by SERB. Only applicable in Stage 1 (Pilot), Stage 2 and Stage 3 (up to interim analysis two).
Stage 1		Stage 1 refers to the Pilot Stage of the trial. Please see section 3.2 for the Pilot Stage Summary of Completion.
Stage 2		Stage 2 is beyond the Pilot Stage and up to the first interim analysis.

Term	Abbreviation	Description
		See section 3.3 for Stage 2 Summary of Completion (First Interim Analysis)
Stage 3		Stage 3 is beyond the first interim analysis and up to the second interim analysis. See section 3.4 for Stage 3 Summary of Completion (Second Interim Analysis)
Stage 4		Stage 4 is beyond the second interim analysis and up to final analysis.

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 several 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.

Trial Design

Multi-arm, multi-stage (MAMS), pragmatic, multicentre, randomised controlled trial, with an internal pilot, exploring the use of several specific in-theatre interventions, used alone or in combination, to reduce the rates of SSIs. A non-factorial design with allocations to various combinations of the trial interventions to be used during the same operation.

Trial Setting

At least 60 NHS hospitals in the UK will participate in **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%; 33% relative reduction) 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 assisted) with a planned incision of at least 5cm are eligible. Patients must be able and willing to give written informed consent and be available for a wound assessment at day 30-37.*

Exclusion Criteria

Patients with a previous laparotomy within 3 months prior to randomisation, pregnant or breast feeding and wounds not closed primarily.

**Patients with a new or documented allergy/intolerance to any of the trial interventions (chlorhexidine) will not be randomised to an arm containing this intervention, but will still be eligible for recruitment to other arms of the trial.*

Interventions

Several health technologies will be assessed versus the control arm (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 sponge at closure, versus no sponge

Please note: In January 2022, following the first interim analysis, arms including intervention 2 – Iodophor-impregnated incise drape (arms C, E, G and H) were closed to recruitment.

In January 2023, following the second interim analysis, arms including intervention 3 – Gentamicin-impregnated sponge (arms D and F) were closed to recruitment.

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 wound complication rate (Clavien-Dindo classification).
- Serious Adverse Events up to 30 days (wound or intervention-related only).
- 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 EQ-5D-5L) measured at Baseline, Day 7 (or discharge if sooner) and Day 30.
- Cost effectiveness (Resource Use Questionnaire (RUQ))

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?

Summary of arms currently open to recruitment (Protocol V4.0)

ARM	INTERVENTION	SUMMARY	FROM PROTOCOL VERSION
A	NONE (Control)	All patients undergoing an abdominal operation will have their skin prepared using some form of antiseptic skin preparation. Only in participants randomised to the trial intervention of 2% Alcoholic Chlorhexidine (arms B or F) should this skin preparation be used. For all other participants, they should receive the surgeon's choice of skin preparation as long as this is NOT 2% Alcoholic Chlorhexidine. 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.	V1.0
B	SKIN PREP	2% alcoholic chlorhexidine skin preparation	V1.0

Summary of arms closed to recruitment (Protocol V4.0)

ARM	INTERVENTION	SUMMARY	TO PROTOCOL VERSION
C	DRAPE	Iodophor-impregnated incise drape	V2.0
D	SPONGE	Gentamicin-impregnated sponge	V3.0
E	SKIN PREP and DRAPE	2% alcoholic chlorhexidine skin preparation and Iodophor-impregnated incise drape	V2.0
F	SKIN PREP and SPONGE	2% alcoholic chlorhexidine skin preparation and Gentamicin-impregnated sponge	V3.0
G	DRAPE and SPONGE	Iodophor-impregnated incise drape and Gentamicin-impregnated sponge	V2.0
H	SKIN PREP and DRAPE and SPONGE	2% alcoholic chlorhexidine skin preparation and Iodophor-impregnated incise drape and Gentamicin-impregnated sponge	V2.0

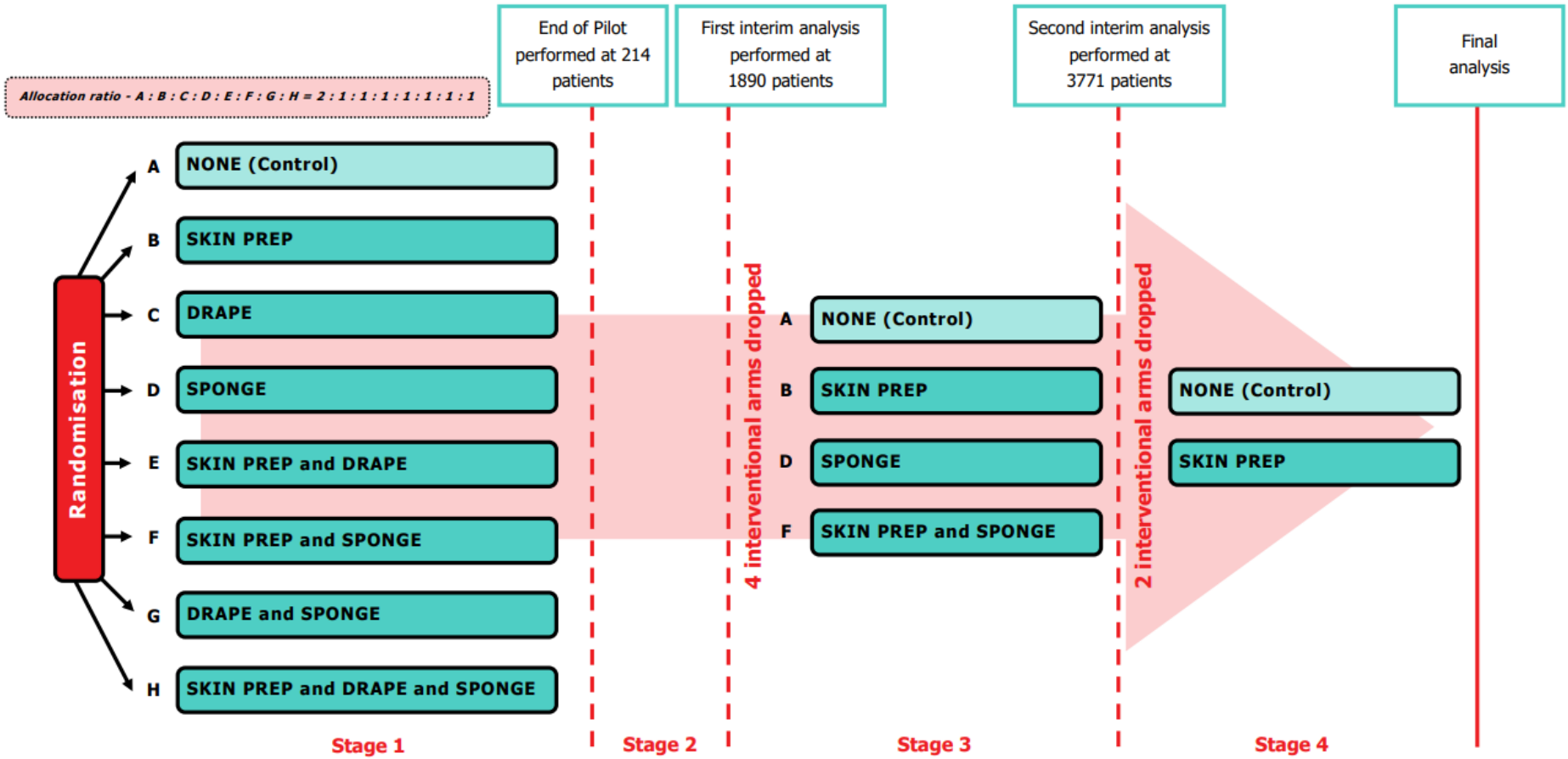
TRIAL SCHEMA

Figure 1.0

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

Intervention 2 - Iodophor-impregnated incise drape [DRAPE]

Intervention 3 - Gentamicin-impregnated collagen sponge [SPONGE]



Randomisation will cease to arms demonstrating a lack of effectiveness or lack of benefit compared to the control arm.

TABLE OF CONTENTS

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 ensures 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 drop (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 outcome 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 in 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 an ongoing 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 being assessed in this trial, considering current NHS policy. The three relevant guidelines to this trial 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)

All of the interventions chosen to be assessed in **ROSSINI 2** 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 trial 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 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 (as at trial commencement in early 2018):

- 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 that showed significantly lower SSI in the chlorhexidine alcohol group than in the povidone-iodine group (50). However, this trial has been criticised for having a non-pragmatic control group; our survey data suggests that few hospitals use 2% alcoholic chlorhexidine routinely in abdominal surgery (47).

Guidelines update – NICE guideline Surgical site infections: prevention and treatment [NG125] was an update to the previous CG74, and was released in April 2019:

- A thorough review of the available evidence around skin preparation options, including a network meta-analysis was performed. To quote directly from the guidelines: *"Based on the evidence, the committee agreed that an alcohol-based solution of chlorhexidine should usually be the first choice when deciding which antiseptic preparation to use. However, the quality of the studies was not good enough for the committee to make a strong recommendation for the choice of antiseptic preparation."*
- No recommendation was made regarding the optimal strength of chlorhexidine (i.e. 0.5% versus 2%) – in fact a **research recommendation** was issued as follows: *"What is the clinical and cost effectiveness of chlorhexidine in alcohol at different concentrations in the prevention of surgical site infection when applied to the skin before incision?"*. We are likely to provide additional evidence to address this question within ROSSINI 2.

(2) Iodophor-impregnated incise drapes

Please note: In January 2022, following the first interim analysis, arms including intervention 2 – Iodophor-impregnated incise drape (arms C, E, G and H) were closed to recruitment.

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

Supplier: 3M Infection Prevention

Guidelines (as at trial commencement in early 2018):

- 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).

Guidelines update – NICE guideline Surgical site infections: prevention and treatment [NG125] was an update to the previous CG74, and was released in April 2019:

- Incise drapes were not re-considered in this guidelines update; no new recommendations were made.

(3) Gentamicin-impregnated sponge

Please note: In January 2023, following the second interim analysis, arms including intervention 3 – Gentamicin-impregnated sponge (arms D and F) were closed to recruitment.

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 (as at trial commencement in early 2018):

- 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/ sponges 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/ sponge versus placebo or nothing across all types of surgery in 6979 patients (54). Overall the implants/ sponges 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/ sponge 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).

Guidelines update – NICE guideline Surgical site infections: prevention and treatment [NG125] was an update to the previous CG74, and was released in April 2019:

- The following important guideline was issued: "*Only apply an antiseptic or antibiotic to the wound before closure as part of a clinical research trial.*"
- The reasoning and rationale behind this statement was summarised as follows: "*The committee agreed that the evidence was not current or clear enough to make a recommendation on the use of topical antiseptics and antibiotics before wound closure. The committee also considered concerns about antimicrobial resistance and the potential for multidrug resistance, and agreed that without new conclusive evidence, use of intraoperative topical antibiotic and antiseptics should be stopped. They agreed that this is an important area for further research and recommended that they should be considered only in the context of further research to help limit unnecessary use and determine their clinical effectiveness. They also developed a research recommendation to determine the clinical and cost effectiveness of applying antiseptics and antibiotics before wound closure.*"
- This research recommendation is directly relevant to, and supportive of, ROSSINI 2 being undertaken. It was worded thus: "*is the application of antiseptics and antibiotics in the operative field before wound closure, clinically and cost effective in reducing surgical site infection rates?"*

1.3. COVID-19

On 11th March 2020, the World Health Organization declared the international spread of COVID-19 to represent a global pandemic. The unprecedented impact the pandemic had on the NHS and wider UK society means that there will be long-reaching or even permanent changes to the NHS structures for delivering both patient care and clinical research. As a result of these, we had amended some trial processes and pathways in **ROSSINI 2** to ensure that the trial remains safe and practicable, whilst protecting the scientific and methodological integrity of the trial.

These changes had been necessary in the following aspects of the trial: 1) secondary objectives; 2) trial entry criteria and 3) patient follow-up pathways.

2. AIMS AND OBJECTIVES

ROSSINI 2 is a multi-arm, multi-stage (MAMS), pragmatic, 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 (Stage 1)

2.1.1. Aims

The aims of the internal pilot trial were to assess:

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

The internal pilot aimed to recruit 150 patients across 10 sites.

2.1.2. STOP/ GO Criteria

The following STOP-GO criteria was assessed at 6 months post-start of recruitment 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 stage.
- **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 stage.

See Section 3.2: Pilot Stage Summary of Completion (Stage 1)

2.2. Main Phase III Trial

2.2.1. Primary Objective

To determine whether several 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 used alone, or in various combinations 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?
    - operation approach (laparoscopic-assisted, open)?
    - SARS-CoV-2 virus status on day of surgery (swab positive; negative; not tested)?
    - SARS-CoV-2 antibody status on day of surgery (antibody positive; negative; not tested)?

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

- What is the impact of SARS-CoV-2 virus infection status on overall SSI rate, and in those who previously had COVID-19 (proven or suspected), is there a time-dependent impact upon overall SSI rates?

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 several 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 interventions to be used during the same operation.

3.2. Pilot Stage Summary of Completion (Stage 1)

The Independent Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) held a joint meeting on 30th September 2019 to review the internal pilot stage objectives and results. They were satisfied with the progress against the predefined progression criteria and recommended that **ROSSINI 2** continue to the main phase of the trial without the need for any major modifications. The NIHR also reviewed trial progress and reports from the oversight committees; they confirmed progression to the main phase in October 2019. The table below details the success of the internal pilot stage.

STOP / GO Criteria	Aim	Actual	Achieved
Recruitment	Open 10 sites	14	✓
	Recruit 150 patients	216	✓
	6 of the 10 sites to achieve an average recruitment of 4 patients per month.	9 of the 14 sites opened achieved an average of 4 patients per month.	✓
Adherence	Investigators' adherence to arm allocation must be at least 80%.	92.8%	✓
Follow-up	Data submission within 60 days of randomisation should be at least 70%.	81%-100%	✓

3.3. Stage 2 Summary of Completion (First Interim Analysis)

It was agreed in an extraordinary meeting of the Trial Management Group (TMG), TSC and DMC on October 5th 2021 (and subsequently by the Funder) that it would be reasonable to bring forward the first interim analysis i.e. sooner than 2357 patients as originally planned. This decision was based on observing a slightly higher than expected **overall** event rate.

On December 15th 2021, the results of the first interim analysis were presented and reviewed by the independent DMC. They made the recommendation to drop the intervention arms containing Intervention 2, Iodophor-impregnated incise DRAPE. The DMC recommendations were discussed by the ROSSINI 2 TMG, independent TSC, Sponsor and Funder at a meeting

on January 7th 2022. Following this meeting, it was agreed that the following arms containing Intervention 2, Iodophor-impregnated incise DRAPE, would close to recruitment:

Arm C	DRAPE
Arm E	SKIN PREP & DRAPE
Arm G	DRAPE & SPONGE
Arm H	SKIN PREP & DRAPE & SPONGE

All other aspects such as the primary objective, trial design, trial setting, outcome measures and key eligibility criteria remain unchanged.

3.4. Stage 3 Summary of Completion (Second Interim Analysis)

A total of 3771 participants had been randomised – of whom 952 were randomised to arms that had been dropped after the last DMC, leaving 2819 randomised participants in the trial; 1108 to the control arm and approximately 570 to each of the intervention arms. Of these, 973 controls and approximately 500 in each intervention have primary outcome data available for analysis at this interim analysis giving a total of 2475 people for analysis.

On January 25th 2023, the results of the second interim analysis were presented and reviewed by the independent DMC. They made the recommendation to drop the intervention arms containing Intervention 3, Gentamicin-impregnated SPONGE. The DMC recommendations were discussed by the independent TSC, the ROSSINI 2 TMG and Sponsor at a meeting on January 31st 2023. Following the meeting, it was agreed that the following arms containing Intervention 3, Gentamicin-impregnated SPONGE, would close to recruitment:

Arm D	SPONGE
Arm F	SKIN PREP & SPONGE

All other aspects such as the primary objective, trial design, trial setting, outcome measures and key eligibility criteria remain unchanged.

3.5. Stage 4 of ROSSINI 2

The health technologies that will be assessed in Stage 4 versus the control arm (standard care):

1. 2% alcoholic chlorhexidine skin preparation, versus any other standard skin preparation

3.6. Trial Setting

At least 60 NHS hospitals in the UK will participate in **ROSSINI 2.**

3.7. 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. **ROSSINI 2** is also participating in the NIHR Associate PI scheme – for more details see section 23.

3.8. Patient and public involvement

This trial has been developed in partnership with patient representatives and service users, from the Birmingham Surgical Research Patient Forum. Patient representatives sit on the TMG and the TSC 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 stages 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).

3.9. 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 20 of this protocol.

3.10. Assessment of Risk

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

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

The interventions being assessed in the trial are already being used by a small number of surgeons nationally and internationally. They are all commercially available and approved for use in the UK. In the absence of level 1 evidence, current behaviours for SSI reduction practice are influenced by surgeon experience and hospital policies governing local availability. As a pragmatic trial, **ROSSINI 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.

There are no additional COVID-19 risks from participation in **ROSSINI 2**. All patients entering the trial will have already had a decision made to undergo surgery (in either an elective or emergency context) and undergone appropriate local clinical pathways such as swabbing and self-isolation to mitigate their overall risks from COVID-19; there are no additional direct risks from the trial pathways, interventions or wound assessments if a patient also participates in **ROSSINI 2**.

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

(1) Pre-operative discussions about the trial and provision of PIS
(2) Consent to participate in the trial
(3) QoL questionnaire (EQ-5D-5L) at Baseline (pre-op)
(4) In-theatre randomisation
(5) Use of the intraoperative intervention(s), unless allocated to control arm
(6) An in-person (in-patient) wound review by a blinded, trained observer and a QoL questionnaire (EQ-5D-5L) at Day 7 (or pre-discharge if sooner).
(7) Another wound review (either in person or by video consultation, telephone can be used as a last resort) by a blinded, 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 (WHQ).
(8) Completion of the Resource Use Questionnaire (RUQ) at Day 30. This will give information regarding the costs that have been incurred in relation to the patient's wound healing (only applicable in final stage of **ROSSINI 2**). Sites will be informed when this part of the trial is to be implemented.
(9) If there is an ongoing SSI at day 30, the patient will be requested to complete the EQ-5D-5L, WHQ and RUQ every 30 days until the infection has resolved. They will not need to undergo any further trial related wound assessments beyond 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. It is also essential that any staff carrying out a wound assessment must complete the wound assessment training prior to conducting any patients' assessments of their wound. Below is a link to the wound assessment training:

https://bctu-redcap.bham.ac.uk/surveys/?s=DFPM7YMKRJ

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 trained in a standardised application technique.

4.2. Inclusion Criteria

- Patients undergoing an abdominal operation, these include colorectal, hepatobiliary, upper GI, urological, vascular, or gynaecological operations
- Patients undergoing an abdominal operation (open or laparoscopic assisted) with a planned incision of at least 5cm
- Patients aged 16 years or older
- Patients able and willing to undergo a wound assessment at day 30-37 after surgery
- 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
- Known to be pregnant or currently breast feeding
- Operations where the wound is not anticipated to be closed primarily

4.4. Notes on Eligibility Criteria

- SARS-COV-2 virus status and antibody status on day of surgery – all patients are eligible to enter the trial regardless of positivity, negativity or not tested status.
- Patients with a new or documented allergy/ intolerance to the trial intervention(s) (chlorhexidine) will not be randomised to an arm containing this intervention, but will still be eligible for recruitment to other arms of the trial.
- Purely groin incisions such as inguinal hernia repair or vascular access of the femoral vessels do not count as abdominal surgery and are not eligible to enter the trial.

Participants who potentially fulfil the inclusion criteria for this trial must have their eligibility confirmed by an appropriately delegated member of the local 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 and if the local hospital/ practice allows this as per their own policy.

Each individual patient should **not** undergo a second randomisation to **ROSSINI 2** within 3 months post-surgery and until the previously randomised wound has fully healed.

4.5. 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 trial. Sites should contact the **ROSSINI 2** Trials Office to discuss this prior to co-enrolment.

5. CONSENT

It will be the responsibility of the Principal Investigator (or delegate if local site allows) to obtain written informed consent for each participant prior to performing any trial related procedures. Consent may also be taken by 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 and other allied health professionals can also obtain consent if local practice allows and this responsibility has been delegated by the PI and again, captured on the **ROSSINI 2** Site Signature and Delegation Log.

All eligible patients will be approached for recruitment to **ROSSINI 2**. A Patient 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 and the patient will be blinded to the allocation
- What the trial will involve for the participant
- The anticipated benefits and potential risks of taking part in the trial
- The patient will not be offered reimbursement of any expenses occurred as a result of participating in **ROSSINI 2**
- That participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time.

The participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team if they wish. The participant has the opportunity to ask questions before signing and dating the latest version of the **ROSSINI 2** Informed Consent Form (ICF). The ICF will be completed using one of the following processes:

- **Face-to-face (Preferred method)**

  The ICF is given to the participant and they will initial, sign and date the ICF. The PI or delegate consenting the participant will then sign and date the ICF. Only after the PI or delegate has countersigned the ICF is consent considered to be obtained.

- **By post/ email/ telephone**

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

When emailing or posting, copies of all correspondence/ letters between the participant (with the attached partially completed ICF) and from the person receiving consent (with the fully completed ICF attached) are to be printed and stored with the ICF.

A copy of the completed ICF will be given/posted/emailed to the participant, a copy will be filed in the medical notes and the original placed in the Investigator Site File (ISF). In addition, if the participant has given explicit consent, a copy of the signed ICF will be sent to the **ROSSINI 2** trials team for review upon request.

Detailed instructions on postal/email consent can be found within your ISF.

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.

Once the participant is entered (randomised) into the trial, the participant's unique trial number (TRIAL ID) will be entered on the ICF and maintained in the ISF.

Details of the informed consent discussions will be recorded in the participant's medical notes. Stickers can be provided upon request, such discussions (and stickers) 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, consent process followed (post, email or face-to-face) and date consent received.

At each visit (including any follow-up that is conducted remotely), 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 (if required). 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 **ROSSINI 2** 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, SCREENING AND RANDOMISATION

6.1. Recruitment

Patients will be identified as potential participants at the time they are listed for surgery by a surgeon, surgical trainee, consultant or nurse. It is envisaged that the 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 and electronic theatre lists.
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 can 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 trial will be obtained pre-operatively 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 on 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.

6.3. Randomisation

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

Randomisation will be via a secure online randomisation system (available at https://w3.abdn.ac.uk/hsru/ROSSINI2) or via 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 and Trial allocation 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 intervention arms. Each research arm will specify a single intervention or combination of interventions that will be allocated and used during that specific operation. These interventions will be applied by the operating team as per the trial protocol and each site will be given trial specific training during site set-up to ensure homogeneity.

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

- Centre
- Urgency (planned, unplanned)
- Predicted contamination (clean, clean-contaminated, contaminated, dirty)
- Stoma (yes – pre-existing, yes – formed during this operation, no)

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;
- 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. Immediately following randomisation, a confirmatory, blinded e-mail from CHaRT will be sent to selected members of the Research Team. The **ROSSINI 2** trial team will receive a randomised allocation confirmatory e-mail. At site, only the person who randomised the participant into the trial will also receive this unblinded email.

The randomisation allocation, or use of the interventions used within the trial, should not be entered on the operation record or patient notes. Instead, stickers are provided in the **ROSSINI 2** ISF which should be added to the patient notes to explain that the patient is in a blinded trial.

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 combination 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 were any deviations from the randomised allocation why this occurred.

Investigators will keep a **ROSSINI 2** Patient Recruitment and Identification Log which links patients with their allocated trial number. Site Staff must maintain this document, which is not for submission to the Trials Office. Site Staff 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 on a monthly basis or 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 an observer-blinded 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. The **ROSSINI 2** Trial office will supply participating sites with stickers to be used in the patient's medical notes to confirm that the patient is in a clinical trial and who to contact in the event of a medical emergency which necessitates unbinding.
- 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.
- CRFs that contain blinded information should be stored elsewhere to avoid accidental unblinding of those carrying out wound assessments.

6.6. Unblinding

Patients can be unblinded upon request at the end of the trial, which is once the final patient has completed all follow-up and the database is locked for final analysis.

7. TRIAL INTERVENTIONS

7.1. Usual care and site requirements

All patients undergoing an abdominal operation will have their skin prepared using some form of antiseptic skin preparation. Only in participants randomised to the trial intervention of 2% Alcoholic Chlorhexidine (arm B) should this skin preparation be used. For all other participants, they should receive the surgeon's choice of skin preparation as long as this is NOT 2% Alcoholic Chlorhexidine. 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.

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 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 videos 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.

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.

Comparator 1: All patients undergoing an abdominal operation will have their skin prepared using some form of antiseptic skin preparation. Only in participants randomised to the trial intervention of 2% Alcoholic Chlorhexidine (arms B or F) should this skin preparation be used. For all other participants, they should receive the surgeon's choice of skin preparation as long as this is NOT 2% Alcoholic Chlorhexidine. 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. The **ROSSINI 2** In-Theatre Form will collect which skin prep was used in the control arm and ensure compliance to the randomised allocation.

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

Please note: In January 2022, following the first interim analysis, arms including intervention 2 – Iodophor-impregnated incise drape (arms C, E, G and H) were closed to recruitment.

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
- Gently 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 at 180 degrees, back on itself and away 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 a separate appendix.

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

Intervention 3: Gentamicin-impregnated sponge *(SERB)*

Please note: In January 2023, following the second interim analysis, arms including intervention 3 – Gentamicin-impregnated sponge (arms D and F) were closed to recruitment.

This intervention describes the implantation of Gentamicin-impregnated collagen sponges at the time of fascial closure. Each sponge (5 by 20 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 sponge can be cut to size through the sterile packaging whilst dry
- Ensure all gloved hands or instruments are free of blood before handling the sponge
- 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 sponge 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 sponge should be used and closure of the subcutaneous tissues and skin should be performed according the surgeon's standard practice.

7.3. Contraindications

An investigator must confirm the patient's eligibility to be randomised to each of the interventions at the time of randomisation. If a patient is not able to receive a trial intervention, 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 **ROSSINI 2** Trial Office.

If a patient has a new or documented allergy or intolerance to Chlorhexidine then the patient is not eligible to participate in **ROSSINI 2.**

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.

Intervention 2: Iodophor Antimicrobial Incise Drape *(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 sponge *(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.
- Bovine collagen comes from cows and is the most common source of collagen in medical supplements and implants. After harvesting the cattle for their meat, the cow hides (skins) are removed and then treated to extract their collagen protein. All cellular material and DNA is removed. Patients will be informed of this via the PIS and should they not be willing to be randomised to receive this intervention, they will not be able to enter the trial.

7.4. Accountability and Compliance Procedures

It is important to ensure that patients receive the allocated interventions and that they 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.
(2) The number and resupply of trial interventions will be monitored by the **ROSSINI 2** Trials Team and assessed against expected levels whenever a reordering request is required, or delayed.

The **ROSSINI 2** Trials Team 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 interventions are used in a homogenous and reproducible manner by all surgeons and sites, standardised training materials have been created.

7.5. Cessation of Treatment/ Continuation after the Trial

The 2.0% Alcoholic Chlorhexidine skin preparation intervention is applied intraoperatively.
Patients who undergo re-laparotomy or wound exploration 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).
If any trial intervention is withdrawn from the trial for a safety reason, randomised patients would be alerted immediately and appropriate, reparative safety measures will be taken. At this point, 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 the **ROSSINI 2** Trials Team. An initial supply of the interventions will be

delivered to each site prior to site opening. It will then be the responsibility of the **ROSSINI 2** Trials Team to arrange for resupply, delivery and redistribution. The process for this will be explained during the Site Initiation Visit.
The trial interventions (or box in which they are held) will be marked with a label "For **ROSSINI 2** Trial Use Only". The labels will be provided in the ISF and are available from the **ROSSINI 2** Trial Office should sites require additional supplies.

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 /sponges
(SERB)

7.6.2. Packaging, Labelling and Storage

All interventions will be stored in a secure, clean, dry place free from damp at room temperature and within the supplied sterile packaging. No specific special requirements are required above the standard storage conditions of theatre products and refrigeration will not be necessary. Any excess intervention material will be disposed of in the hospital's standard clinical waste bins as per local hospital protocol. Interventions 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, asked to withdraw from the trial or be asked for reimbursement.

8. OUTCOME MEASURES AND TRIAL 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 wound complication rate (Clavien-Dindo classification).
- Wound or intervention only related 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 EQ-5D-5L) at Baseline, Day 7 (or discharge if sooner) and Day 30.
- Cost effectiveness (Resource Use Questionnaire; RUQ).

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 wound complication rate

The 30-day postoperative wound 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's wound and is not either a treatment failure or sequel, is a complication. The Clavien-Dindo classification determines the severity of a complication based on the therapeutic consequence of that complication (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 at Day 7 or at discharge if sooner and another at Day 30 mirroring the timings of blinded wound assessment. If the patient has an ongoing SSI 30 days post-operatively, then the EQ-5D-5L questionnaire will be completed every 30 days until the wound has fully healed (e.g. Day 60, Day 90, Day 120 etc.).

8.2.1.4. Cost-effectiveness

Cost effectiveness will be assessed using the Resource Use Questionnaire (RUQ) 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 trial (1). As we are now in the final stage (Stage 4) of **ROSSINI 2** and approaching the final analysis, the RUQ will be implemented and utilised.

8.3. Schedule of Assessments

Visit	Pre-operative (Elective and emergency surgery)	At surgery	Day 7 wound review (To be completed as an inpatient on Day 7, or discharge if sooner) ±2 days	Day 30 wound review (To be completed as an outpatient, between Day 30-37)	Ongoing SSI (every 30 days until resolution)
Eligibility confirmation	X				
Patient Information Sheet provided	X				
Written Informed Consent[+]	X	X	X	X	X
Baseline (BASELINE CRF & CONTACT CRF)	X				
Randomisation (RANDOMISATION CRF)		X			
Operation (IN-THEATRE CRF)		X			
Blinded Wound Assessment / review (WOUND ASSESSMENT CRFs)			X*	X**	
Readmissions for surgery (RETURN TO THEATRE CRF)		X[++]			
Serious Adverse Event Reporting (SAE CRF)		X			
Questionnaires:					
Quality of Life Questionnaire (EQ-5D-5L)	X^		X	X	X
Wound Healing Questionnaire (WHQ)				X	X
Resource Use Questionnaire (RUQ)[$]				X	X

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

* Wound assessment data collected here should be applicable and relevant between Day 0 (day of surgery) to Day 7 Wound Assessment (or up to discharge).

** Wound assessment data collected here should be applicable and relevant between Day 7 (first wound assessment) to Day 30 Wound Assessment (second wound assessment). Data should not be duplicated over forms. If no previous wound assessment has occurred, then data collected should be from Day 0 to Day 30.

[++] Only to be completed if patient is required to return to theatre (within 30 days post-surgery) for any reason.

^ Quality of Life at Baseline should be completed after Consent but before Surgery.

[$] RUQ will only be collected on those participants in the final stage of the trial. We are now in the final stage (stage 4) of ROSSINI 2 and approaching the final analysis, the RUQ should be implemented and utilised.

8.4. Trial Follow-Up Assessments

Participant retention will be maximised by minimising deviation from the usual postoperative patient pathway. If an in-person wound assessment is not possible, the protocol does allow for a wound assessment to be conducted using real-time telemedicine remote video consultation. Telephone follow up assessments and data captured via routinely collected data documented in the patients' medical records, of the wound can be used as a last resort.

8.4.1. Pre-discharge/ Day 7 Wound Review

To be performed at day 7 (assessment window: days 5 to 9), or within one day of discharge (if sooner), by a blinded, in-person wound assessor. The wound will be assessed for an infection according to the CDC SSI criteria, since the day of surgery.
The assessment will be undertaken by a member of the research team or clinical investigator who has been trained in the diagnosis of wound infections and who is blinded to the randomised allocation. These delegates must be tasked this role, have undergone the wound assessment training (https://bctu-redcap.bham.ac.uk/surveys/?s=DFPM7YMKRJ) and have signed the **ROSSINI 2** Site Signature and Delegation Log prior to carrying out any wound assessments.
It is recommended that at this time point, patients should be given a Patient Reminder Card (PRC) to inform them of their upcoming Day 30 Wound Assessment. Please refer to section 8.5 for more information on PRCs.
As part of this wound assessment, the Wound Assessment (Day 7) CRF will be completed.

8.4.2. Day 30 Wound Review

To be performed 30 days post-operation (assessment window days 30-37; with day 0 being the day of surgery) by a blinded, in-person wound assessor. If a direct face-to-face wound assessment is not possible for whatever reason, this wound assessment is to be conducted using real-time telemedicine remote video consultation. If neither of these follow-up methods are possible, telephone follow up assessments and data captured via routinely collected data documented in the patients' medical records, of the wound can be used as a last resort. The wound will be assessed for an infection according to the CDC SSI criteria and since the previous wound assessment. If no previous wound assessment has occurred (at Day 7), then data collected should be from Day 0 to Day 30. Data should not be duplicated over CRFs.

This assessment will be undertaken by a member of the research team or clinical investigator 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. As part of this wound assessment, the Wound Assessment (Day 30) CRF will be completed.

To maximise the fidelity of the follow-up period between discharge and the Day 30 Wound Assessment, a patient-reported Wound Healing Questionnaire (WHQ) will be completed at the Day 30 follow-up visit in conjunction with the researcher's wound assessment. The WHQ is a single patient and observer measure for post-discharge SSI assessment. It contains 18 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). Patients may also be asked to complete the RUQ, this will give information regarding the costs that have been incurred in relation to the patient's wound. The RUQ will only be collected on those participants in the final stage of the trial. Sites will be notified when to implement this.

Participants will be made aware of the requirement for a 30-day follow-up assessment before informed consent is taken. In exceptional circumstances where a patient becomes unable or unwilling to attend a follow-up appointment in person or via telemedicine video consultation at 30-days, every effort will be made to complete the WHQ (and any other questionnaires) by telephone as a last resort. 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 assessments

The wound will be assessed by a blinded, experienced individual, trained in this role who has signed the **ROSSINI 2** Site Signature and Delegation Log. Outcome assessments will be undertaken by individuals 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 (https://bctu-redcap.bham.ac.uk/surveys/?s=DFPM7YMKRJ). This system will reduce inter-observer variability and make an inherently subjective endpoint as reliable and reproducible as possible.

8.4.4. Follow-up beyond the Primary Trial Window

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

- Completion of the EQ-5D-5L questionnaire
- Completion of the WHQ
- Completion of a RUQ

These questionnaires at these time points will be completed with the patient via the telephone or sent via the post by staff at site.

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. Patient Reminder Cards

The purpose of these cards is to inform patients of their upcoming Day 30 Wound Assessment. Informing a patient in advance of their future assessment should prevent patient drop-out and withdrawals.

8.6. Withdrawal / Change of Status

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.

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

Participants are able to withdraw (cease participation) from the following aspects of the **ROSSINI 2** trial:

- Surgery
- Follow Up (Wound Assessments at Day 7 & Day 30)
- Patient reported Questionnaires
- Ongoing SSI Follow Up (QoL, WHQ & RUQ)
- All of the above

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

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

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

9. ADVERSE EVENT REPORTING

9.1. Definitions

Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research interventions.
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 Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.
** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

9.2. Adverse Event recording - General

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA).

Definitions of different types of AEs are listed in the table above.

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

9.2.1. Adverse Event (AE) reporting in ROSSINI 2

The reporting period for AEs in **ROSSINI 2** will be from the day of surgery (when the interventions were administered) until the end of trial follow-up (30 days later).
AEs are commonly encountered in participants undergoing colorectal, hepatobiliary, upper GI, urological, vascular, or gynaecology operations. As the safety profiles for this trial population and the interventions used in this trial are well characterised, and will not affect the safety of participants, a strategy of targeted reporting of AEs will be used.
Only (expected) AEs that are infection and wound complication related will be recorded on the relevant CRFs as part of the outcome measures for this trial, these include:

Infection related:

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

Complication related:

- Granuloma
- Haematoma
- Seroma
- Dehiscence

9.2.2. Serious Adverse Event (SAE) reporting in ROSSINI 2

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

1. **Record safety reporting - exempt SAEs** in the medical notes but **not report** them to the trials office on an SAE form (or any other CRFs) as per Section 9.2.2.1.

2. **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 9.2.2.2.

3. **Report SAEs to the trial office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above categories must be reported as per Section 9.2.2.3.

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

9.2.2.1. Serious Adverse Events not requiring reporting to the Trial Office

At whatever time they occur during an individual's participation, from randomisation to the end of participant follow-up, the following are not considered to be critical to evaluations of the safety of the trial:

- 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.

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

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

Where the safety profile is well established, the causal relationship between the participant's underlying condition or surgery, and the SAE, may be known. That is, such events are protocol-defined as "expected".

Such events should still be reported in the patient's medical records and on the relevant CRFs, but do not require expedited reporting on an SAE Form (immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined;

- Death (unrelated to the trial/ intervention(s))
- Interventions (either within theatre, radiology department or on the ward) to drain 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
- Prolonged hospital stay as a result of wound infections
- Wound complications
- Surgical site infections

9.2.2.3. Serious Adverse Events requiring expedited reporting to the Trial Office

The following SAEs (that are <u>related to the use of each intervention (or the control)</u>) should <u>always</u> be recorded and reported (within 24 hours) to the BCTU Trials Office as a SAE, on the In-Theatre Form and SAE Form:

- Death (related to the trial/ intervention(s))
- Skin reactions
- Allergic reactions
- Combustion

Participants may suffer from other complications from their surgery or their underlying condition but if these are unrelated to their wound and/or the intervention(s), they do not need to be reported on a SAE Form even if they meet the usual criteria of an SAE.

If a participant has experienced any of these prior to receiving any of the intervention(s) then they do not need to be reported as an SAE.

Any other SAEs that are related and unexpected would require expedited reporting to the trial office.

9.3. SAE Reporting Process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE Form, the PI (or delegate) should 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 PI or delegate(s) must complete, date and sign the **ROSSINI 2** SAE Form. The completed form together with any other relevant, appropriately anonymised, data 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

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

On receipt of an SAE Form, the **ROSSINI 2** Trials Team will allocate each SAE a unique reference number and notify the site via email as proof of receipt. The site and the **ROSSINI 2** 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.

If the site has not received confirmation of receipt of the SAE from the **ROSSINI 2** Trials Team or if the SAE has not been assigned a unique SAE identification number within 1 working day, the site should contact the **ROSSINI 2** Trials Team.

9.4. Assessment of causality of an SAE

When completing the SAE Form, the PI (or delegate) will be asked to define the nature of the seriousness and causality (relatedness, see Table 3) of the event.

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

As per Table 3 all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trials office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

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. Categories of causality

On receipt of an SAE Form, the Trial Office will forward it, with the unique reference number, to the CI (or delegate), who will independently* review the causality of the SAE. An SAE judged by the PI or CI (or delegate) to have a reasonable causal relationship with the trial intervention will be regarded as a related SAE. The severity and causality assessment given by the PI will not be downgraded by the CI (or delegate). If the CI (or delegate) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, both opinions will be provided with the report.

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

9.4.1. Assessment of expectedness of an SAE by the CI

The CI (or delegate) will also assess all related SAEs for expectedness with reference to the criteria in Table 4 below.

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information.
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

Table 4. Categories of expectedness

If the event is unexpected (i.e., it is not defined in the protocol as an expected event) it will be classified as a related and unexpected SAE.

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

9.4.2. Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the Trial Office and the original kept in the ISF.

9.4.3. 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. We have also excluded pregnancies and breastfeeding individuals from the trial and for these reasons, pregnancies will not be monitored for any potential SAEs.

9.5. Reporting SAEs to third parties

The independent DMC may review any SAEs at their meetings.

The Trial Office will submit a progress report to the REC annually starting 12 months after the date of the favourable opinion was given. An electronic copy should be emailed to the REC within 30 days of the end of the reporting period.

The Trial Office will report all events categorised as Unexpected and Related SAEs to the Research Ethics Committee (REC) and UoB Research Governance Team (RGT) within 15 days of being notified.

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.

9.6. Emergency Unblinding

Emergency unblinding will only be permitted for urgent clinical/ medical reasons (e.g. severe allergy) or patient safety issues. This can be done by all investigators involved in participant care by contacting the Trial Office Monday to Friday, 9:00 to 17:00 UK time, except for bank holidays, government guided closures and University of Birmingham (UoB) closed days.

In case of an out-of-hours emergency, the named person who randomised and/or operating surgeon should be contacted for the allocation and the **ROSSINI 2** Trials Office should be notified at the earliest available opportunity.
If it becomes necessary to unblind, where possible, members of the site research team will remain blinded, subject to clinical need.

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.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data are kept as part of the participants' medical notes (paper or electronic) and will be accessible and maintained at site.

Typically, the data provided on all CRFs should routinely be recorded in the patient's medical notes, when this is not being conducted then data collected for the purpose of **ROSSINI 2** can be recorded on the paper CRFs. Data should then be transcribed to REDCap and the data on paper will be considered the source data, and should subsequently be filed in the ISF.

10.2. Data handling during paper phase of ROSSINI 2

For the paper phase of **ROSSINI 2**, sites recorded data on paper CRFs, data clarifications were raised on paper DCFs and then the originals were sent to the **ROSSINI 2** trials office. The copies were kept at the local site. The trials office were responsible for transcribing the data from the originals into the electronic CRF. The electronic CRF is held on a secure REDCap database at Birmingham Clinical Trials Unit.

10.3. Data handling during electronic phase of ROSSINI 2

For the electronic phase of **ROSSINI 2**, all data and any data clarifications will be entered 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 will there be simultaneous input of data to a form by both the **ROSSINI 2** Trial Team and staff at site.

10.4. Case Report Form (CRF) Completion

Case Report Form (CRF) definitions:

Baseline:

Basic demographic data including date of birth, NHS number, sex, BMI, comorbidity etc

Contact Form:

Contains contact information including the patient's name

Randomisation Form:

Contains all details required to randomise a patient including pre-operative predictions.

In-Theatre Form:

Theatre data including interventions used and operative details etc

Wound Assessment (Day 7 or before discharge):

First blinded wound review

Wound Assessment (Day 30):

Second blinded wound review

Return To Theatre Form:

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

EQ-ED-5L:

Quality of Life Questionnaire, to be completely at Baseline, Day 7, Day 30 and Ongoing SSI if applicable.

Wound Healing Questionnaire:

The intervening period (Day 7-30) covered by a patient self-reported Wound Healing Questionnaire (WHQ) to be completed at Day 30 and Ongoing SSI if applicable.

Resource Use Questionnaire:

Health resource usage will only be collected on those participants in the final stage of the trial. Once implemented, to be completely at Day 30 and Ongoing SSI if applicable.

Change of Status Form:

Details the change of a patient's status, reason for change and level of data collected.

SAE Form:

Details of an event that meets the definition of an SAE and requires expedited reporting.

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. 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/unknown data
- Completing SAE forms and reporting SAEs
- Protocol and GCP non-compliances

In all cases it remains the responsibility of the site's PI (or delegate) 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 (or delegate), on the paper CRF (per form) during the paper phase and/or on the eCRF (per patient) during the electronic phase of the trial.

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 surgery), Day 7 (or discharge if sooner), Day 30 and only if applicable, every 30 days until the present wound infection has fully healed. Participants will also be asked to complete the Wound Healing Questionnaire (WHQ) at Day 30 and if applicable, every 30 days until the patient's wound infection 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 has been discharged, and has provided consent, research staff at site may telephone a participant and complete all questionnaires by proxy.

10.6. Data Management

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

Entries on the paper CRFs should ideally be made in ball point pen, ideally 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 paper CRFs, or data entered in REDCap, for compliance with the protocol, data consistency, missing data and timing.

Data reported on each CRF (paper or electronic) 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. Queries (in REDCap) and Data Clarification Forms (DCFs) will be generated on a regular basis by **ROSSINI 2** trial office staff and sent to the site for clarification.
In all cases, it remains the responsibility of the Principal Investigator (or delegate) to ensure that the CRF has been completed correctly and that the data are accurate. PIs (or delegates) will be required to sign off on all patients.

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

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

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

The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database 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 Trial Centre (University of Birmingham).
- 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

Archiving will be authorised by the **ROSSINI 2** Trial office on behalf of the Sponsor following submission of the end of trial report. 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 10 years. No documents will be destroyed without prior approval from the Trials Office on behalf of the sponsor.

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. The Site Signature and Delegation Log should be kept up to date. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation either by a meeting or a tele/video-conference, 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, 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 or high 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 BCTU.

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 (when requested) and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent DCFs or queries in REDCap requesting missing data or clarification of inconsistencies or discrepancies at a frequency and intensity determined by the Data Management plan.

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 or local audits.

11.4. Notification of Protocol Non-Compliances and Serious Breaches

11.4.1. General Definitions of a Non-compliance

A **Protocol Non-Compliance** is defined as any:

- violation of GCP or a violation in accordance with the ROSSINI 2 Protocol or relevant trial specific guidelines.
- deviation or departure from an approved protocol.

A **Continuing Non-compliance** is a series of more than one noncompliant event, in reasonably close proximity that indicates the need for evaluation of the methods and systems used to ensure accurate and reliable data collection as part of the trial. Continuing non-compliance need not involve a sequence of similar events if the events, taken as a whole, indicate that examination of the methods and systems used is warranted. This can also include, in extreme circumstances, the need for evaluation of the methods and systems used to protect human subjects.

A combination of continuing non-compliances may result in a serious breach.

11.4.2. General Definitions of a Serious Breach

A **Serious Breach** is a noncompliant event that has or had the potential to:

- impact rights, welfare or safety of present, past or future subject(s),
- increase the risks and/or decrease the benefit for research subjects(s), or
- compromise the integrity of the trial data

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 six months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection, data input and data cleaning in preparation for the database to be locked for the clinical data analysis. 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 (e.g. 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 however 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 – overall summary

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 4 stages, one pilot stage, two interim analyses, and one final analysis. At each interim analysis, we have planned that at least two research arms will not randomise any further patients. Therefore, the maximum number of research arms in the trial will reduce from 7 to at most 5 after the first interim analysis, and subsequently to a maximum of 3 after the second interim analysis. The first interim analysis is planned once approximately 2350 patients have joined the trial and the second interim 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.

This total recruitment number has been calculated under the assumption that only two research arms are dropped at each interim analysis. The calculation takes into account the number of formal comparisons being analysed throughout the trial, because large numbers of comparisons can lead to spurious statistically significant results. If more than 2 arms are dropped at an interim analysis, then the trial as a whole will require fewer comparisons and thus the total recruitment number may need to be modified. Any recalculation of the sample size (due to greater than planned numbers of arms being dropped from the trial) will only be carried out after the second interim analysis, when the number of arms progressing to final analysis is known.

Overall sample size	Approximately 6610 patients across all arms and stages
Total number of stages	4 stages (including pilot stage)
Total number of arms	8 arms at the beginning (1 control, 7 research arms) At most, 6 arms after interim analysis 1 (1 control, at most 5 research) At most, 4 arms after interim analysis 2 (1 control, at most 3 research)
Allocation ratio	2:1 = Control : Research
Primary Outcome Measure	Proportion of patients reporting Surgical Site Infections up to 30 days after surgery.
Control arm SSI rate at 30 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%

Table 7. Overall sample size and design assumptions

13.1.4. Sample size calculation – design assumptions

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 4-5 patients per month per site represents a conservative estimate.

Allocation ratio: During Stage 1 and Stage 2, 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 following an interim analysis, the 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.

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).

Time to decision: We anticipate that the time to decision about continuing or stopping recruitment to the research arms will be approximately 4 months: For the first and second interim analyses, once the target number of patients is recruited, it is expected that around 4 months will pass 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, DMC and 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	150	No sample size target	6 months	8	N/A	N/A	N/A
2	2357	2357	402/201	19 months	8	0.40 [94%]	0.004 [0.0254]	85%
3	4632	4108	854/427	27 months	6	0.14 [94%]		
4	Approx. 6610	4915+	1887/944	33 months**	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 was planned for the pilot stage to last 6 months and to recruit approximately 150 patients. Formal sample size calculation is not applicable for the pilot stage. Please see section 3.2 for the Pilot Stage Summary of Completion.

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 arm patients will have been recruited due to the (a) 4 months' time period 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 close to further randomisations at Stages 2 and 3, and arms which will continue until the end of the trial. The sample size may be recalculated after the second interim analysis if more than the minimum 2 arms are dropped at either of the interim analyses.

Recruitment and trial duration: Based on the initial recruitment assumption, it was expected that recruitment would 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 stage). However, due to the impact of the COVID-19 pandemic, these timelines have been extended.

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 (SAP) 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 6.3.1 (except centre as many centres are expected to randomise only a few patients) 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 a sufficient number of patients have contributed data to the primary outcome analysis (see section 13.1.4). 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). An adjusted risk difference and an adjusted relative risk and the associated 95% confidence interval will be estimated from a Poisson model with robust error variances. 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. An adjusted absolute risk difference and adjusted relative risk ratio, and the associated 95% confidence intervals, will be estimated from a Poisson model with robust error variances. 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 risk difference and adjusted relative risk, and the associated 95% confidence intervals, will be estimated from a Poisson model with robust error variances. The p-value from the associated chi-squared test will be produced and used to determine statistical significance.

Continuous Outcomes (e.g 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 for the primary outcome only. These will be examined by including an intervention group by subgroup interaction parameter in the regression model, and will be presented alongside the effect estimate and 95% confidence interval 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

The first and second formal interim analyses will include efficacy data alongside other important aspects such as adherence and acceptability, to enable the DMC to determine which arms to recommend being dropped. At least two research arms will be dropped from the trial after each interim analysis.

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 being assessed in the trial. Actual uptake and compliance to randomised allocation will be formally assessed at the end of the pilot stage, 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 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 (i.e. they are either used or they are not), limiting the opportunities for changes in practice within the trial.

13.4. 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 trial database and validated as being ready for analysis.

14. 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. To avoid collecting large amounts of data from trial participants in those arms that would eventually become obsolete, health economic analysis will start in the final stage of the **ROSSINI 2** to provide assessment of the most effective trial interventions.

14.1. 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.

14.2. 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.

14.3. 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 trial 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 items (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.

15. TRIAL ORGANISATIONAL STRUCTURE

The Chief Investigator will have overall responsibility for the trial. 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 trial, 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 trial-specific staff to manage the trial for the project duration. The trial manager will undertake all day-to-day conduct of the trial with oversight provided by a trials management team leader. Given the size and complexity of the trial, a senior data manager and a data manager 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 trial. 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 (if required), an independent surgeon and a clinical trialist. The Independent DMC 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 trial progresses.

15.1. Sponsor

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

15.2. Coordinating Centre

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

15.3. 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.

15.4. Trial Steering Committee

A TSC will be created for the **ROSSINI 2** Trial and meet via tele/video-conference or face-to-face, as required depending on the needs of the trial 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 TSC is to provide the overall supervision of the trial, including the practical aspects of the trial. Membership of the TSC is listed at the front of the protocol. The TSC will monitor trial progress and conduct, and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC or equivalent and ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy.

15.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants.

The DMC will operate in accordance with a trial specific **ROSSINI 2** DMC 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:

- Review of the Pilot Stage - this was not a formal interim analysis and no analyses of efficacy occurred, however the DMC reviewed progress against the Pilot Stage objectives and approved the continuation of the trial into the Main Phase.
- First interim analysis at 2357 patients
- Second interim analysis at 4632 patients
- Final analysis at approximately 6610 patients

Please note: Number of patients and stages may be subject to change.

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.

16. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, the applicable UK Acts of Parliament and Statutory Instruments, (and relevant subsequent amendments) which include, but are not limited to, the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Data Protection Act 2018.

The trial will be carried out according to the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the main REC prior to 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.

17. 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 Data Protection Act 2018 (and subsequent amendments).

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 (upon request). This will be used to perform central monitoring of the consent process.

The PI 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.

18. FINANCIAL AND OTHER COMPETING INTERESTS

ROSSINI 2 is an investigator-initiated and investigator-led trial funded by the NIHR Health Technology Assessment Programme. All interventions, including training are provided free-of-charge by BD Infection Prevention (Skin Prep), 3M Infection Prevention (Drape) and SERB (Sponge).
The trial design, data collection, analyses and interpretation of the findings remain under control of the TMG. No competing interests are declared.
Members of the TSC and DMC are required to provide declarations on potential competing/conflicts of interests as part of their membership of the committees.

19. 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.

20. SUB-STUDIES

20.1. 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.

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 available 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.

21. ACCESS TO FINAL DATA SET

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses.

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

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

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

22. PUBLICATIONS AND OUTPUTS

22.1. 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** Trial Group; West Midlands Research Collaborative". The writing group, trial management group, TSC, DMC, 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 trial will qualify an investigator for co-authorship status.

22.2. Publications and impact

This complex trial 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 trial course. As such, planning a publication schedule is difficult and the TMG will likely choose 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.

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 trial results after the Final Trial Report had been compiled and/or after the paper describing the primary outcome had been published.

22.3. 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 trial and then a plenary session to report results.

23. Associate Principal Investigator Scheme

One principal investigator and at least one associate principal investigator (API) per surgical specialty open will be permitted at each site. The first site principal investigator to register will hold overall responsibility for the site trial conduct, and will be responsible for submitting a final authorship list from each site. Multiple APIs per site will be permitted, providing they complete their six-month minimum tenure and achieve formal API sign-off by the NIHR co-ordinating centre. The API will undertake a variety of defined roles including: supporting trial approvals, helping with site set-up, co-ordinating within team communication, recruitment, co-ordination of other trial team members and support Birmingham Clinical Trials Unit (BCTU) to ensure that all members of the trial team have completed mandatory training, and signed the delegate log. For more information on the API scheme please see: https://www.nihr.ac.uk/documents/associate-principal-investigator-pi-scheme/25040

24. Reference List

1. Pinkney TD, Calvert M, Bartlett DC, Gheorghe A, Redman V, Dowswell G, et al. Impact of wound edge protection devices on surgical site infection after laparotomy: multicentre randomised controlled trial (ROSSINI Trial). Bmj. 2013;347:f4305.
2. Jansen TC, Kompanje EJ, Bakker J. Deferred proxy consent in emergency critical care research: ethically valid and practically feasible. Crit Care Med. 2009;37(1 Suppl):S65-8.
3. Smyth ET, McIlvenny G, Enstone JE, Emmerson AM, Humphreys H, Fitzpatrick F, et al. Four country healthcare associated infection prevalence survey 2006: overview of the results. J Hosp Infect. 2008;69(3):230-48.
4. Leaper DJ, van Goor H, Reilly J, Petrosillo N, Geiss HK, Torres AJ, et al. Surgical site infection - a European perspective of incidence and economic burden. Int Wound J. 2004;1(4):247-73.
5. Leaper DJ, Edmiston CE, Jr., Holy CE. Meta-analysis of the potential economic impact following introduction of absorbable antimicrobial sutures. Br J Surg. 2017;104(2):e134-e44.
6. Kirkland KB, Briggs JP, Trivette SL, Wilkinson WE, Sexton DJ. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol. 1999;20(11):725-30.
7. Gheorghe A, Moran G, Duffy H, Roberts T, Pinkney T, Calvert M. Health Utility Values Associated with Surgical Site Infection: A Systematic Review. Value Health. 2015;18(8):1126-37.
8. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol. 1999;20(4):250-78; quiz 79-80.
9. Tanner J, Khan D, Aplin C, Ball J, Thomas M, Bankart J. Post-discharge surveillance to identify colorectal surgical site infection rates and related costs. J Hosp Infect. 2009;72(3):243-50.
10. Smith RL, Bohl JK, McElearney ST, Friel CM, Barclay MM, Sawyer RG, et al. Wound infection after elective colorectal resection. Ann Surg. 2004;239(5):599-605; discussion -7.
11. Astagneau P, Rioux C, Golliot F, Brucker G. Morbidity and mortality associated with surgical site infections: results from the 1997-1999 INCISO surveillance. J Hosp Infect. 2001;48(4):267-74.
12. Klevens RM, Edwards JR, Richards CL, Jr., Horan TC, Gaynes RP, Pollock DA, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep. 2007;122(2):160-6.
13. Wilson AP, Gibbons C, Reeves BC, Hodgson B, Liu M, Plummer D, et al. Surgical wound infection as a performance indicator: agreement of common definitions of wound infection in 4773 patients. Bmj. 2004;329(7468):720.
14. Ortiz H, Armendariz P, Kreisler E, Garcia-Granero E, Espin-Basany E, Roig JV, et al. Influence of rescrubbing before laparotomy closure on abdominal wound infection after colorectal cancer surgery: results of a multicenter randomized clinical trial. Arch Surg. 2012;147(7):614-20.
15. Anthony T, Murray BW, Sum-Ping JT, Lenkovsky F, Vornik VD, Parker BJ, et al. Evaluating an evidence-based bundle for preventing surgical site infection: a randomized trial. Arch Surg. 2011;146(3):263-9.

16. Collaborative G. Determining the worldwide epidemiology of surgical site infections after gastrointestinal resection surgery: protocol for a multicentre, international, prospective cohort study (GlobalSurg 2). 2017.
17. Pinkney T, Bartlett D, Gheorghe A, Dowswell G, Morton D, Calvert M. Use of an online e-learning module to standardise the assessment and reporting of a subjective endpoint in a multicentre rct. Trials. 142013. p. P64.
18. Collaborative RoCoSSR, Collaborative WMR. Feasibility study from a randomized controlled trial of standard closure of a stoma site vs biological mesh reinforcement. Colorectal Dis. 2016;18(9):889-96.
19. Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: randomised controlled trial (DREAMS Trial). Bmj. 2017;357:j1455.
20. Rosenthal VD. International Nosocomial Infection Control Consortium (INICC) resources: INICC multidimensional approach and INICC surveillance online system. Am J Infect Control. 2016;44(6):e81-90.
21. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011;377(9761):228-41.
22. Andersson AE, Bergh I, Karlsson J, Nilsson K. Patients' experiences of acquiring a deep surgical site infection: an interview study. Am J Infect Control. 2010;38(9):711-7.
23. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013;13(12):1057-98.
24. NNIfHaC. Surgical site infections: prevention and treatment (CG74). Guidance and guidelines. NICE Guidelines: NICE; 2017.
25. RRE. REF Case study: Surgical Site Infections: Surveillance, Reduction and Prevention: Research Excellence Framework; 2017 [Available from: http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=8073.
26. GGIRF. GIRFT Surgical Site Infection Audit - Getting It Right First Time - GIRFT GIRFT (Getting It Right First Time) 2017 [Available from: https://www.gettingitrightfirsttime.co.uk/cross-cutting-stream/surgical-site-infection-audit/
27. Barratt H, Turner S, Hutchings A, Pizzo E, Hudson E, Briggs T, et al. Mixed methods evaluation of the Getting it Right First Time programme - improvements to NHS orthopaedic care in England: study protocol. BMC Health Serv Res. 2017;17(1):71.
28. Biffi R, Fattori L, Bertani E, Radice D, Rotmensz N, Misitano P, et al. Surgical site infections following colorectal cancer surgery: a randomized prospective trial comparing common and advanced antimicrobial dressing containing ionic silver. World J Surg Oncol. 2012;10:94.
29. Blumetti J, Luu M, Sarosi G, Hartless K, McFarlin J, Parker B, et al. Surgical site infections after colorectal surgery: do risk factors vary depending on the type of infection considered? Surgery. 2007;142(5):704-11.
30. Aimaq R, Akopian G, Kaufman HS. Surgical site infection rates in laparoscopic versus open colorectal surgery. Am Surg. 2011;77(10):1290-4.
31. Ghuman A, Chan T, Karimuddin AA, Brown CJ, Raval MJ, Phang PT. Surgical Site Infection Rates Following Implementation of a Colorectal Closure Bundle in Elective Colorectal Surgeries. Dis Colon Rectum. 2015;58(11):1078-82.

32. Howard DP, Datta G, Cunnick G, Gatzen C, Huang A. Surgical site infection rate is lower in laparoscopic than open colorectal surgery. Colorectal Dis. 2010;12(5):423-7.
33. Serra-Aracil X, Garcia-Domingo MI, Pares D, Espin-Basany E, Biondo S, Guirao X, et al. Surgical site infection in elective operations for colorectal cancer after the application of preventive measures. Arch Surg. 2011;146(5):606-12.
34. Keenan JE, Speicher PJ, Thacker JK, Walter M, Kuchibhatla M, Mantyh CR. The preventive surgical site infection bundle in colorectal surgery: an effective approach to surgical site infection reduction and health care cost savings. JAMA Surg. 2014;149(10):1045-52.
35. Uchino M, Ikeuchi H, Matsuoka H, Takahashi Y, Tomita N, Takesue Y. Surgical site infection and validity of staged surgical procedure in emergent/urgent surgery for ulcerative colitis. Int Surg. 2013;98(1):24-32.
36. Limon E, Shaw E, Badia JM, Piriz M, Escofet R, Gudiol F, et al. Post-discharge surgical site infections after uncomplicated elective colorectal surgery: impact and risk factors. The experience of the VINCat Program. J Hosp Infect. 2014;86(2):127-32.
37. Milsom JW, Smith DL, Corman ML, Howerton RA, Yellin AE, Luke DR. Double-blind comparison of single-dose alatrofloxacin and cefotetan as prophylaxis of infection following elective colorectal surgery. Trovafloxacin Surgical Group. Am J Surg. 1998;176(6A Suppl):46s-52s.
38. Ishida H, Yokoyama M, Nakada H, Inokuma S, Hashimoto D. Impact of oral antimicrobial prophylaxis on surgical site infection and methicillin-resistant Staphylococcus aureus infection after elective colorectal surgery. Results of a prospective randomized trial. Surg Today. 2001;31(11):979-83.
39. Suzuki Y, Kamigaki T, Fujino Y, Tominaga M, Ku Y, Kuroda Y. Randomized clinical trial of preoperative intranasal mupirocin to reduce surgical-site infection after digestive surgery. Br J Surg. 2003;90(9):1072-5.
40. Nakamura T, Kashimura N, Noji T, Suzuki O, Ambo Y, Nakamura F, et al. Triclosan-coated sutures reduce the incidence of wound infections and the costs after colorectal surgery: a randomized controlled trial. Surgery. 2013;153(4):576-83.
41. Parmar MK, Barthel FM, Sydes M, Langley R, Kaplan R, Eisenhauer E, et al. Speeding up the evaluation of new agents in cancer. J Natl Cancer Inst. 2008;100(17):1204-14.
42. Barthel FM, Parmar MK, Royston P. How do multi-stage, multi-arm trials compare to the traditional two-arm parallel group design--a reanalysis of 4 trials. Trials. 2009;10:21.
43. Royston P, Barthel FM, Parmar MK, Choodari-Oskooei B, Isham V. Designs for clinical trials with time-to-event outcomes based on stopping guidelines for lack of benefit. Trials. 2011;12:81.
44. Bratton DJ, Phillips PP, Parmar MK. A multi-arm multi-stage clinical trial design for binary outcomes with application to tuberculosis. BMC Med Res Methodol. 2013;13:139.
45. Organisation WH. WHO. Global guidelines on the prevention of surgical site infection. WHO. 2016.
46. Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017.
47. P D, E R, A W, L S, L B, TD P. A collaborative snapshot audit of current preventative practice in surgical site infection during laparotomy operations. Int J Surg2014. p. S49–S50.

48. Noorani A, Rabey N, Walsh SR, Davies RJ. Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery. Br J Surg. 2010;97(11):1614-20.
49. Zhang D, Wang XC, Yang ZX, Gan JX, Pan JB, Yin LN. Preoperative chlorhexidine versus povidone-iodine antisepsis for preventing surgical site infection: A meta-analysis and trial sequential analysis of randomized controlled trials. Int J Surg. 2017;44:176-84.
50. Darouiche RO, Wall MJ, Jr., Itani KM, Otterson MF, Webb AL, Carrick MM, et al. Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis. N Engl J Med. 2010;362(1):18-26.
51. Webster J, Alghamdi A. Use of plastic adhesive drapes during surgery for preventing surgical site infection. Cochrane Database Syst Rev. 2015(4):Cd006353.
52. Dewan PA, Van Rij AM, Robinson RG, Skeggs GB, Fergus M. The use of an iodophor-impregnated plastic incise drape in abdominal surgery--a controlled clinical trial. Aust N Z J Surg. 1987;57(11):859-63.
53. Tanner J, Kiernan M, Hilliam R, Davey S, Collins E, Wood T, et al. Effectiveness of a care bundle to reduce surgical site infections in patients having open colorectal surgery. Ann R Coll Surg Engl. 982016. p. 270-4.
54. Chang WK, Srinivasa S, MacCormick AD, Hill AG. Gentamicin-collagen implants to reduce surgical site infection: systematic review and meta-analysis of randomized trials. Ann Surg. 2013;258(1):59-65.
55. Bennett-Guerrero E, Pappas TN, Koltun WA, Fleshman JW, Lin M, Garg J, et al. Gentamicin-collagen sponge for infection prophylaxis in colorectal surgery. N Engl J Med. 2010;363(11):1038-49.
56. Lovering AM, Sunderland J. Impact of soaking gentamicin-containing collagen implants on potential antimicrobial efficacy. Int J Surg. 2012;10 Suppl 1:S2-4.
57. KK V, TD P, K N, D L, AG A. Gentamicin-impregnated collagen implants for the reduction of surgical site infections (Protocol). Cochrane Database of Systematic Reviews2014.
58. Staniszewska S, Brett J, Simera I, Seers K, Mockford C, Goodlad S, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. Bmj. 2017;358:j3453.
59. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387(10024):1163-77.
60. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36(5):309-32.
61. Berard F, Gandon J. POSTOPERATIVE WOUND INFECTIONS: THE INFLUENCE OF ULTRAVIOLET IRRADIATION OF THE OPERATING ROOM AND OF VARIOUS OTHER FACTORS. Ann Surg. 1964;160(Suppl 2):1-192.
62. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med. 2009;360(5):491-9.
63. NICE NIfHaCE. Gentamicin, BNF: British National Formulary [CorporatePage]. NICE; 2014 [updated 2014-08-05. Available from: https://bnf.nice.org.uk/drug/gentamicin.html.

64. Macefield RC, Reeves BC, Milne TK, Nicholson A, Blencowe NS, Calvert M, et al. Development of a single, practical measure of surgical site infection (SSI) for patient report or observer completion. J Infect Prev. 2017;18(4):170-9.
65. Reeves BC, Andronis L, Blazeby JM, Blencowe NS, Calvert M, Coast J, et al. A mixed-methods feasibility and external pilot study to inform a large pragmatic randomised controlled trial of the effects of surgical wound dressing strategies on surgical site infections (Bluebelle Phase B): study protocol for a randomised controlled trial. Trials. 2017;18(1):401.
66. Bluebelle Study Group tSaPAaRCfS, and the West Midlands Research Collaborative: BLUEBELLE. Bluebelle study (phase A): a mixed-methods feasibility study to inform an RCT of surgical wound dressing strategies. BMJ Open. 2016;6(9):e012635.
67. Palmqvist CL, Ariyaratnam R, Watters DA, Laing GL, Stupart D, Hider P, et al. Monitoring and evaluating surgical care: defining perioperative mortality rate and standardising data collection. Lancet. 2015;385 Suppl 2:S27.
68. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.
69. Matthews JH, Bhanderi S, Chapman SJ, Nepogodiev D, Pinkney T, Bhangu A. Underreporting of Secondary Endpoints in Randomized Trials: Cross-sectional, Observational Study. Ann Surg. 2016;264(6):982-6.
70. LAPCO. LAPCO National Training Programme in Laparoscopic Colorectal Surgery lapco.nhs.uk2017 [Available from: http://lapco.nhs.uk/activity-latest-HES-data.php.
71. Goumard C, Farges O, Laurent A, Cherqui D, Soubrane O, Gayet B, et al. An update on laparoscopic liver resection: The French Hepato-Bilio-Pancreatic Surgery Association statement. J Visc Surg. 2015;152(2):107-12.
72. Strong VE, Devaud N, Karpeh M. The role of laparoscopy for gastric surgery in the West. Gastric Cancer. 2009;12(3):127-31.
73. Itatsu K, Sugawara G, Kaneoka Y, Kato T, Takeuchi E, Kanai M, et al. Risk factors for incisional surgical site infections in elective surgery for colorectal cancer: focus on intraoperative meticulous wound management. Surg Today. 2014;44(7):1242-52.
74. Shaffer VO, Baptiste CD, Liu Y, Srinivasan JK, Galloway JR, Sullivan PS, et al. Improving quality of surgical care and outcomes: factors impacting surgical site infection after colorectal resection. Am Surg. 2014;80(8):759-63.
75. Drosdeck J, Harzman A, Suzo A, Arnold M, Abdel-Rasoul M, Husain S. Multivariate analysis of risk factors for surgical site infection after laparoscopic colorectal surgery. Surg Endosc. 2013;27(12):4574-80.
76. NRC NRC. Recognising contributions to work in research collaboratives: Guidelines for standardising reporting of authorship in collaborative research. Int J Surg. 2017.
77. Training JCoS. Joint Committee on Surgical Training: Specialty Advisory Committees (SACs) www.jcst.org2017 [Available from: http://www.jcst.org/committees/specialty-advisory-committees-sacs-1.
78. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-7.

25. Table of Appendices

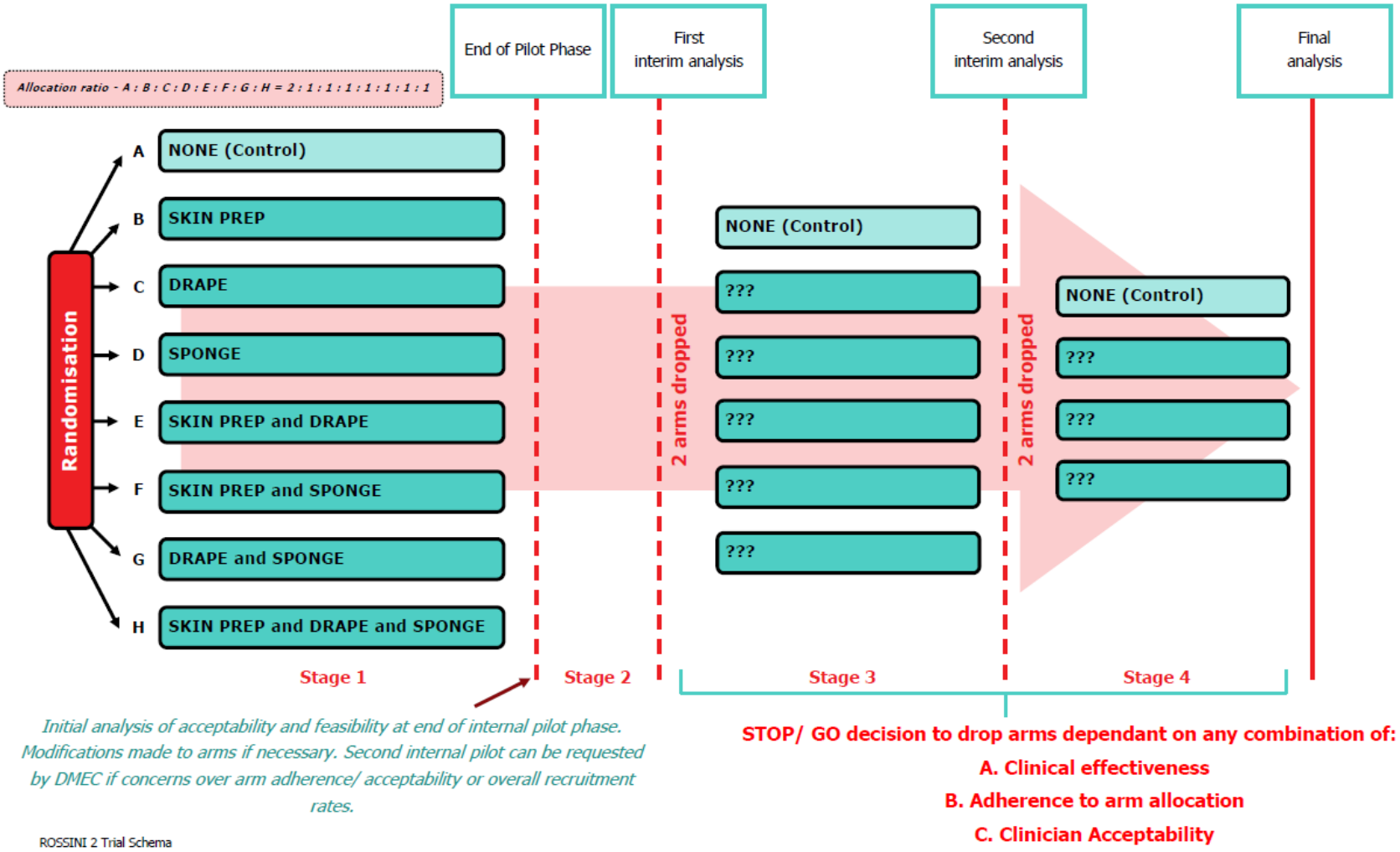
Appendix 1	**Superseded Trial Schema (Stage 1 and 2)**
Appendix 2	**Superseded Trial Schema (Stage 3)**

Appendix 1. Superseded Trial Schema (Stage 1 and 2)

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

Intervention 2 - Iodophor-impregnated incise drape [DRAPE]

Intervention 3 - Gentamicin-impregnated collagen sponge [SPONGE]

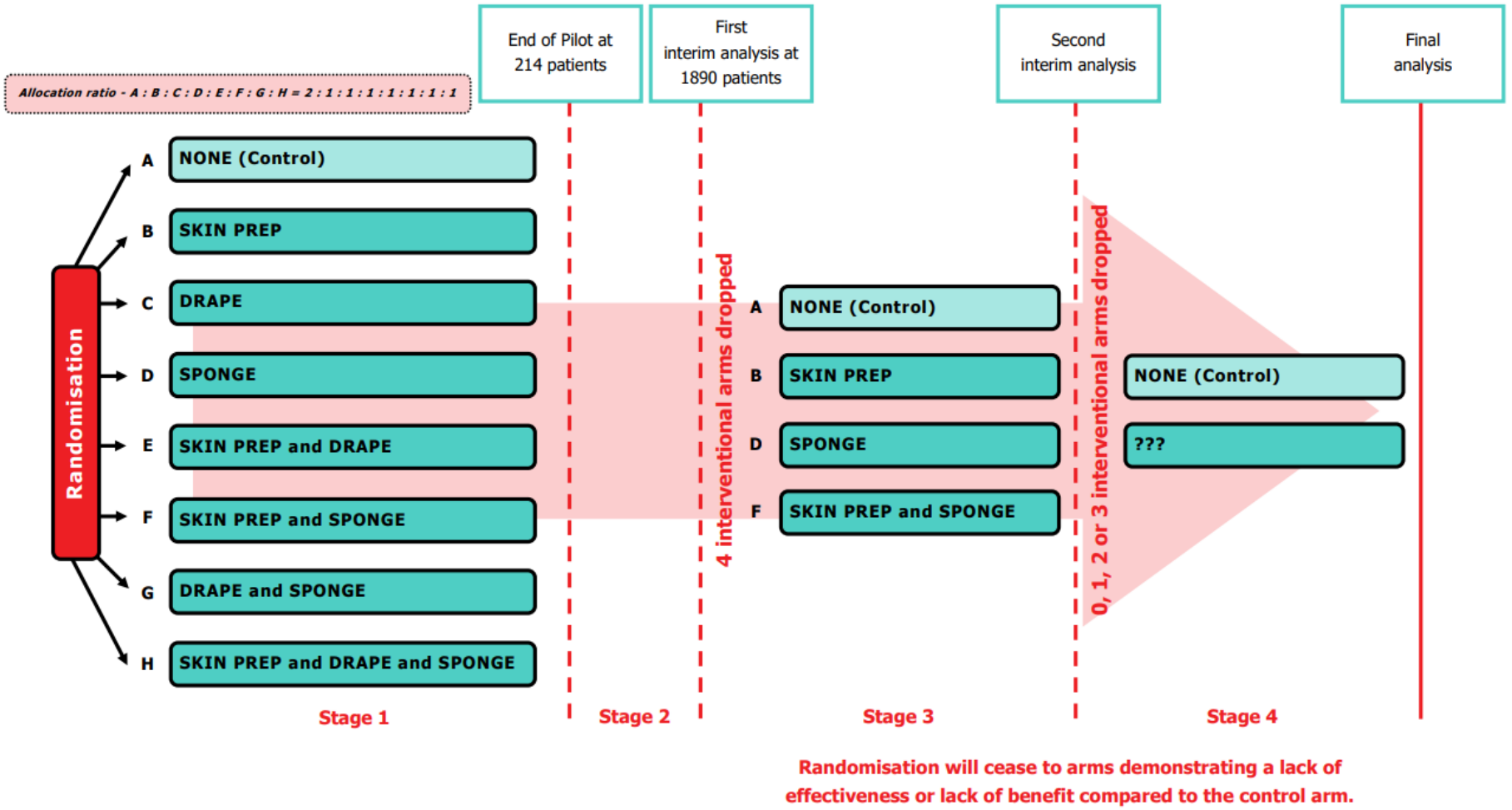


Appendix 2. Superseded Trial Schema (Stage 3)

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

Intervention 2 - Iodophor-impregnated incise drape [DRAPE]

Intervention 3 - Gentamicin-impregnated collagen sponge [SPONGE]



Randomisation will cease to arms demonstrating a lack of effectiveness or lack of benefit compared to the control arm.