ROCSS

ROCSS: Reinforcement of Closure of Stoma Site

A randomised controlled trial of reinforcement of closure of stoma site using a biological mesh

A randomised controlled trial from the West Midlands Research Collaborative

Protocol v8.0

12th January 2021

Protocol Summary

The ROCSS Trial was completed with 2 year follow up and published in The Lancet in 2020. A short summary is below:

Methods

ROCSS took place in 37 hospitals across three European countries (35 UK, one Denmark, one Netherlands), patients aged 18 years or older undergoing elective ileostomy or colostomy closure were randomly assigned using a computer-based algorithm in a 1:1 ratio to either biological mesh reinforcement or closure with sutures alone (control). Training in the novel technique was standardised across hospitals. Patients and outcome assessors were masked to treatment allocation. The primary outcome measure was occurrence of clinically detectable hernia 2 years after randomisation (intention to treat). A sample size of 790 patients was required to identify a 40% reduction (25% to 15%), with 90% power (15% drop-out rate).

Findings

Between Nov 28, 2012, and Nov 11, 2015, of 1286 screened patients, 790 were randomly assigned. 394 (50%) patients were randomly assigned to mesh closure and 396 (50%) to standard closure. In the mesh group, 373 (95%) of 394 patients successfully received mesh and in the control group, three patients received mesh. The clinically detectable hernia rate, the primary outcome, at 2 years was 12% (39 of 323) in the mesh group and 20% (64 of 327) in the control group (adjusted relative risk [RR] 0·62, 95% CI 0·43–0·90; p=0·012). In 455 patients for whom 1 year postoperative CT scans were available, there was a lower radiologically defined hernia rate in mesh versus control groups (20 [9%] of 229 *vs* 47 [21%] of 226, adjusted RR 0·42, 95% CI 0·26–0·69; p<0·001). There was also a reduction in symptomatic hernia (16%, 52 of 329 *vs* 19%, 64 of 331; adjusted relative risk 0·83, 0·60–1·16; p=0·29) and surgical reintervention (12%, 42 of 344 *vs* 16%, 54 of 346: adjusted relative risk 0·78, 0·54–1·13; p=0·19) at 2 years, but this result did not reach statistical significance. No significant differences were seen in wound infection rate, seroma rate, quality of life, pain scores, or serious adverse events.

Interpretation

Reinforcement of the abdominal wall with a biological mesh at the time of stoma closure reduced clinically detectable incisional hernia within 24 months of surgery and with an acceptable safety profile. The results of this study support the use of biological mesh in stoma closure site reinforcement to reduce the early formation of incisional hernias.

There was no significant difference in the quality of life for patients at two years following stoma closure, nor was inserting mesh found to be cost effective. We are now undertaking 5-8 year follow-up of the ROCSS patients in order to assess if there is a quality of life improvement following mesh reinforcement of the closure of stoma site, and whether using mesh is cost effective in the long term. The details of this follow-up study can be found in section 19 of this protocol.

ROCSS was developed by the West Midlands Research Collaborative and the University of Birmingham Clinical Trials Unit

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ROCSS Randomisation

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Clinical queries during office hours should be directed to one of the Clinical Co-ordinators or an appropriate member of the Trial Management Group. Other queries should be directed to the ROCSS study office.

Reference Numbers

Trial sponsor: The University of Birmingham, Edgbaston, Birmingham B15 2TT
Sponsor Reference: RG_11-186
ISRCTN number: 46330337 **ClinicalTrials.gov Identifier:** NCT02238964
IRAS Project ID: 77075 **REC number:** 12/WM/0187
Protocol version: 8.0 (12th December 2021)

Funding and Support in Kind

Funder: NIHR **Funding Scheme:** RfPB **Funder's reference number:** NIHR212020
Funder: NIHR **Funding Scheme:** RfPB **Funder's reference number:** PB-PG-1014-35079
Funder: Allergen (formerly LifeCell, Acelity) **Funding Scheme:** ISS
Funder's reference number: ISIS.10.01.01.DM
Support: Allergen (formerly LifeCell, Acelity); supply of Strattice mesh
This is an investigator-initiated and investigator-led trial. The funders of the trial have no role in trial design, data collection, data analysis or data interpretation.

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CI Signature Page

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

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

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

This protocol has been approved by:

Trial Name: Protocol Version Number:	Version: 8.0
Protocol Version Date:	12 / Jan / 2021
CI Name:	Dion Morton
Trial Role:	Chief Investigator
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement:

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

PI Signature Page

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

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

This protocol has been approved by:

Trial Name: Protocol Version Number:	 Version: 8.0
Protocol Version Date:	12 / Jan / 2021
PI Name: Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

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1. Background

1.1. Incisional hernias at stoma closure sites in context

Abdominal wall hernias are common and are a significant cause of morbidity. Incisional hernias form following closure of the abdominal wall musculature. Incisional hernias at the site of stoma closure form an important and well-defined subgroup for this study. Closure of complex and contaminated abdominal wounds is challenging and carries risks, including wound dehiscence and incisional hernias. In these cases, the hernia rate increases to 50% and may be as high as 80% in certain subgroups[1]. Stoma closure provides a homogeneous subgroup of contaminated complex wound closure for study. Use of biological meshes in this situation may provide a safe method of reducing complications, especially the development of incisional hernias. ROCSS will investigate stoma site closure using biological mesh within the setting of a randomised controlled trial (RCT).

Incisional hernias at stoma sites are a frequent finding, occurring in up to 30% of cases[2-5]. They occur over time and are generally under-reported, which may be due to the elderly nature of the population, the significant co-morbidities or early discharge from follow-up. In up to 10% of cases, patients are submitted to complex re-operation which carries significant morbidity[3 4]. Because of this, many patients will choose not to undergo re-operation. Therefore, low re-operation rates do not necessarily indicate a problem free stoma closure, as re-operations are affected by other factors such as patient age, co-morbidities and patient preference. Incisional hernias are also associated with significant morbidity, which impacts on a person's quality of life, so preventing the development of incisional hernias may improve quality of life for patients. Thus, reinforcement of stoma site closure with a biological mesh may potentially reduce costs in the health service by improving quality of life and reducing the re-operation rate.

1.2. The principle of the ROCSS study

ROCSS is a RCT assessing the placement of a biological mesh at the site of stoma closure on clinical hernia rate. Our hypothesis is that reinforcing the stoma closure site with a collagen mesh is superior to the standard technique in preventing herniation at 2 years.

1.3. The relationship of stomas and hernias

Stomas are commonly constructed following colorectal surgery to protect distal anastomosis or when sepsis prevents primary anastomosis. There is a risk of a wide range of morbidity following both stoma formation and stoma reversal. Morbidity following stoma formation includes stoma complications such as retraction, prolapse, flux and parastomal hernia[5-7]. Complications following reversal include obstruction, wound infection, wound dehiscence, anastomotic leak and the development of incisional hernias[5 7 8]. Hernias are a well-recognised complication with known morbidity[9 10]. They will complicate some wound infections and any wound dehiscence, which in turn can result in secondary small bowel infection. Preventing hernia will also reduce the morbidity from these secondary events

1.4. How frequently do these hernias occur?

A systematic review for this trial exploring hernias at the closure of stoma sites revealed that hernias occur in up to 30% of patients undergoing stoma reversal and that when present, nearly half require subsequent surgical repair. Most of the studies identified as part of this systematic review considered stoma site hernias as a secondary endpoint. The studies that considered it as a primary endpoint showed a higher rate (hernia rate of 30%)[2-4] than the secondary endpoint papers (hernia rate 8%)[11]. Furthermore, when clinical findings and results from CT scans were combined, an even higher incidence was found. It is recognised that over time, incisional hernias can increase in size and become increasingly symptomatic[9]. The data suggests that CT scans may precede the onset of symptoms from the hernias – that is, the CT scan may detect the hernia earlier than the patient will

report it. An exploratory analysis comparing radiological hernia rate with clinical hernia rate will assess this possibility in the ROCSS trial.

There is limited research concerning the post-operative symptoms following stoma site closure, although they may be expected to have a similar profile to incisional and parastomal hernias[9 10]. Such complications include pain and intestinal obstruction, which may necessitate emergency surgery.

The concept of prophylactic prevention of parastomal hernias has been assessed in a small randomised trial, which reported a greater than 50% reduction in herniation[12]. However, prophylaxis of hernias when reversing stomas has not been assessed and a randomised trial is therefore warranted.

1.5. The use of meshes for hernia treatment

Meshes are a well-established treatment for hernias and have also been used prophylactically to prevent hernias forming[13]. Most of these have involved synthetic meshes (e.g. Prolene), and there have been no trials for closed stoma sites.

Prosthetic meshes used at the time of closure of stomas represent an infection risk. Since the bowel has been open at the site, faecal contamination is inevitable, incurring a significant additional morbidity associated with mesh infection. Biological tissue matrices, such as those made from collagen are expected to carry a lesser risk of infection. This is since they are expected to become incorporated into host tissue and prevent the placement of permanent prosthetic material, and as such they represent a way of reducing this infection risk[14], whilst still providing reinforcement to this high risk abdominal wall closure.

1.6. The health economics of ROCSS

At present, biologic meshes are considered to be expensive, but this price will reduce as they are more commonly used. Biological meshes are unlikely to be routinely used, although they may have a place in closure of complex and/ or contaminated abdominal incisions, of which stoma closure is an important and common example. Preventing such incisional hernias will reduce costs in terms of re-operations, future medical contact (hospital and community), appliance use and analgesic use.

1.7. The need for ROCSS: a large, multi-centre, randomised controlled trial

ROCSS is a RCT assessing the placement of a biological mesh in order to reduce the rate of hernias at the site of stoma closure. Strattice® is a well-established biological mesh/ tissue matrix which would be compared against a control arm of no mesh placement.

ROCSS will randomise 790 patients between a biological mesh or standard closure. The primary endpoint will be detection of a clinical hernia at 2 years post randomisation.

We believe that this is an important trial where positive findings will influence future closure of stomas and other complex and/ or contaminated abdominal wounds. This study will also provide useful information on the value of using a CT scan as an early diagnostic tool of herniation, which could then as a surrogate endpoint for clinical hernia in future abdominal wall studies.

2. Trial Design

The ROCSS trial is a prospective, multi-centre RCT.

ROCSS is designed in two stages: i) a feasibility study and ii) a Phase III multi-centre RCT. The assessment of feasibility is being performed as an internal feasibility study within the main phase III RCT.

The feasibility phase showed that patient recruitment and the randomisation process were feasible and that the technique to be used for reinforcement of the stoma closure site with the collagen mesh was deliverable.

The feasibility study has completed successfully and the main phase III trial has followed on directly.

The Phase III study is a prospective, multi-centre RCT to determine if the use of a collagen tissue matrix (Strattice®) reduces the incidence of clinically detectable stoma closure site hernias at two years as compared to standard closure techniques.

The patient and the post-surgical wound assessor will be blinded as to the use of an implant. This will require follow-up to be independent of follow up by the operating surgeon.

2.1. Randomised Comparison

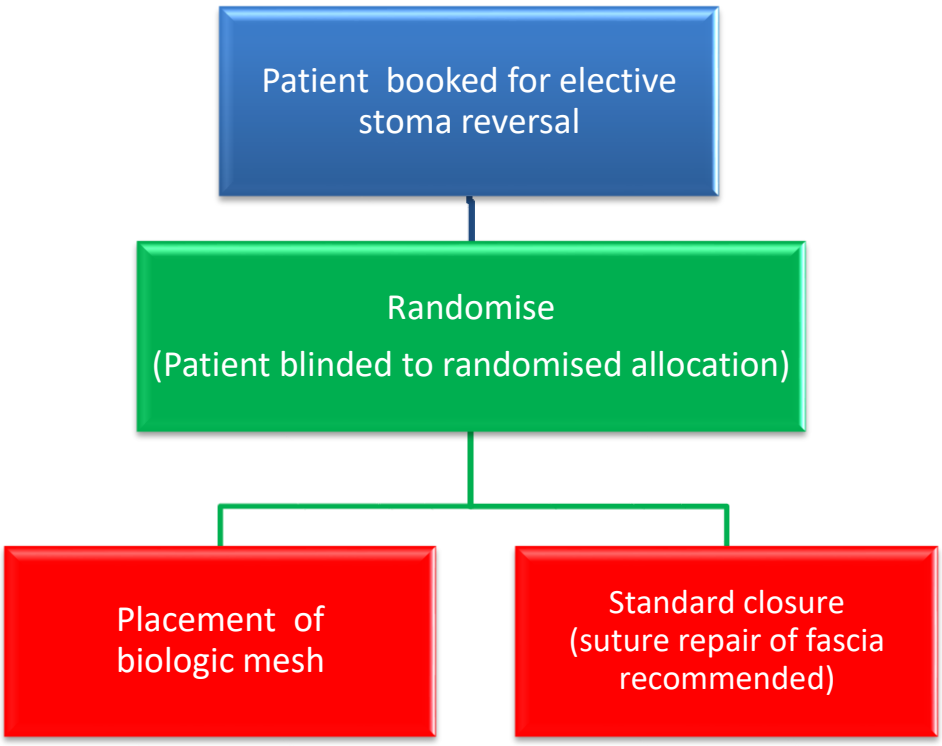
Patients undergoing elective closure of the stoma site will be randomised in a 1:1 ratio between:

Group A: Reinforcement of the stoma closure site using the Strattice collagen mesh

Group B: Control - standard closure without mesh.

All patients undergoing an elective local procedure, laparoscopic assisted procedure or associated laparotomy will be eligible.

2.2. Trial Schema



3. 3. Feasibility Study Objectives and Outcome Measures

3.1. Feasibility Study

The objectives of the feasibility study were:

- To develop strategies for effective recruitment and randomisation
- To assess the deliverability of the mesh placement technique

3.2. Outcome Measures

The outcome measures for the feasibility study were:

1. **Recruitment**

   Recruitment will be measured on a monthly basis. The recruitment plan for the feasibility part will be:

   - Months 1-12:

   5 centres at a rate of one patient per month, over 12 months = 60 patients

   - Months 6-12:

   5 additional centres, one patient per month, over 6 months = 30 patients

   TOTAL: 90 patients

   The above will act as a guide for the ability to recruit into the main trial. Should the target of 90 patients in 12 months not be achieved, this will not preclude continuation to the main phase III trial, but will guide the number of centres that need to be opened for recruitment.

2. **Patient identification and randomisation process**

   Within ROCSS, potential patients can be identified from several clinical settings. The feasibility study will record the percentage of eligible patients screened for entry into the trial and the subsequent acceptance rate as a measure of the success of the process for patient identification and randomisation, seeking acceptability of >50% of eligible patients. A single site technique assessment has successfully consented 7 consecutive patients for mesh insertion, evaluating the Patient Information Sheet and follow-up assessment forms.

3. Deliverability and safety of technique for mesh placement

   Safety will be measured as an assessment of the deliverability of the technique; specifically, the frequency of re-operation, wound infection rates and early clinical hernia occurrences will be recorded. This will be assessed as compared to the control arm. A failure to place implant in >20% of cases would enforce a stopping rule for the trial, and revision of the technique (if appropriate). An independent Data Monitoring and Ethics Committee (DMEC) will be convened after the first 90 patients have been entered into the study or at the end of the 12 month feasibility part whichever occurs first to assess the safety data, and advise on continuation to the main phase III trial.

3.3. 3.3 Results of Feasibility Study

The feasibility study showed that patient recruitment and the randomisation process were feasible and that the technique to be used for reinforcement of the stoma closure site with the collagen mesh is deliverable. We have therefore run seamlessly on from the feasibility study with recruitment for the **main** full phase III trial.

4. Objectives of Main Trial

4.1. Primary Objective

The primary objective of the main phase III ROCSS trial is to assess whether a collagen tissue matrix (Strattice®) reduces the incidence of clinically detectable stoma closure site hernias at two years as compared to standard closure techniques.

4.2. Secondary Objectives

The secondary objectives of the ROCSS trial are to:

- Assess radiological hernia rates at one year post randomisation.
- Assess surgical re-intervention rates.
- Assess the frequency of wound infections and seroma associated with the mesh.
- Assess the impact of the mesh on a patient's quality of life and any pain experienced. Quality of life is an important secondary outcome measure, as the re-operation rate may be low, as even if a clinical hernia is diagnosed, the decision for surgical re-intervention has to take into account the patient's age, any co-morbidities and patient preference.
- Determine the cost effectiveness of the mesh insertion in stoma site closure and management of subsequent hernias.
- Conduct an exploratory analysis to investigate the CT scan as an early surrogate marker of late clinical herniation. Radiological hernia rate at one year post randomisation will be compared with the clinical hernia rate at two years to assess the value of using a CT scan as an early diagnostic tool of herniation. This will identify to other investigators that this is a potential area of clinical need and allow earlier reporting of future studies.

5. Outcome Measures

The outcome measures of the phase III trial will be:

Primary outcome

1. Rate of clinically detectable hernias at two years post-randomisation.

Secondary outcome measures

1. Radiological hernia rate at one year post-randomisation. An exploratory analysis will also compare radiological hernia rate at 1 year with clinical hernia rate at 2 years to assess the value of using a CT scan as an early diagnostic tool of incisional hernias.
2. Incidence of developing a symptomatic hernia evaluated at 12 and 24 months post-randomisation. The clinical detection of hernias defined by palpable fascial defects, and global weaknesses around closed stoma sites without palpable fascial defects, will be recorded. Patient-reported hernia symptoms including a local lump or pain at the site of the stoma closure will also be collected.
3. Surgical re-intervention rates at 2 years post-randomisation.
4. Surgical complications, including wound infections at 30 days post-operatively and at 1 year post-randomisation, and seroma formation at 1 year post-randomisation.
5. Quality of life assessed using EuroQol EQ-5D at baseline, 30 days post-operatively, 12 and 24 months post-randomisation.
6. Pain assessed using a 100 point visual analogue scale at baseline, 30 days post-operatively, 12 and 24 months post-randomisation.
7. Costs per hernia clinically detected at 2 years post-randomisation.
8. Two-year and long-term costs per additional quality adjusted life (QALY) year gained.

Follow-up is assessed from the date of randomisation unless otherwise specified. Surgery is expected to occur on the date of randomisation or preferably within 1 week following randomisation.

Post-operative time points are measured from the date of first surgery.

6. Patient Entry and Eligibility

6.1. Centre Eligibility

Centres, both in the UK and Europe, undertaking colorectal surgery will be eligible to take part in the ROCSS trial. The entry criterion for a site to participate in ROCSS is that surgeons involved in the trial must have performed at least 20 stoma reversals. ROCSS will aim to recruit 790 patients across a minimum of 30 centres.

6.2. Patient Eligibility Criteria

The ROCSS trial will recruit patients who require elective surgery to close either an ileostomy or a colostomy.

The stoma may have been constructed by open or laparoscopic technique. Trephine, midline or laparoscopic approaches are all eligible. Patients with large parastomal hernias in whom the surgeon determines that a mesh repair will definitely be required are not eligible for this trial. However, two mesh sizes will be available (10 x 6cm and 15 x 10cm) for surgeons to use in case of larger defects.

Inclusion criteria

Patients to be included in the ROCSS study must:

- Require an elective closure of an ileostomy or a colostomy. Those patients undergoing a stoma closure involving both a colostomy and an ileostomy element are eligible and should be stratified as colostomy patients.
- Be able and willing to provide written informed consent for the study.
- Be aged 18 years or over.

Exclusion criteria

Patients must be excluded from the ROCSS study, if they are

- Taking part in another clinical study which is related to the surgical procedure.
- Allergic to any porcine or collagen products.
- History of familial adenomatous polyposis, due to increased risk of desmoid tumours.
- The surgeon determines that a mesh repair will definitely be required e.g. due to large parastomal hernia.
- Unable or unwilling to provide written informed consent.

7. Consent and Randomisation

7.1. Informed Consent

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care and International Conference on Harmonisation Good Clinical Practice.

It is envisaged that patients will be recruited from one of three main scenarios:

1. From the colorectal surgery outpatient clinics where elective reversal of the patient's stoma is first discussed with the patient.
2. From the pre-assessment clinic.
3. From planned theatre lists for those patients previously missed at pre-operative assessment. These patients would be approached for entry into the trial at the time of admission for surgery.

An ethically-approved ROCSS patient invitation letter has been provided for use by sites. This letter may be sent to potentially eligible patients, with the PIS to introduce them to the trial prior to their attendance at their next hospital appointment.

Suitable patients will be approached for entry into ROCSS and the rationale for the study explained. The patient will be provided with a written Patient Information Sheet and they will be given the opportunity to ask questions.

Patients must be consented prior to participation in ROCSS, this may be obtained in the outpatient clinic or following admission for surgery. Consent can be taken by consultant surgeons, surgical registrars or trained research nurses.

The original of the consent form should be kept in the ROCSS study site file, copies should then be given to the patient, one kept in the patient's notes and one sent to the ROCSS study office.

When consent has been obtained, the baseline data should be collected using the Randomisation Notepad, and the EuroQoL EQ-5D and the pain VAS questionnaires completed by the patient. This may be in the outpatient clinic or following admission for surgery. The patient can then be randomised into the trial (see below) on the morning of the surgery.

After consent and randomisation, the patient's GP will be informed by letter of their patient's inclusion in the study. The patient's GP will not be told of the randomised allocation. If new information becomes available during the trial which may be relevant to the patient's consent, these forms will be revised and informed consent sought again.

7.2. Re-consent on existing participants

This study will give the patients the option as to when they will find out their randomisation allocation. Patients can either find their randomisation allocation after their participation in the study has completed at 24 months or when the study has finished and the results have been analysed.

- For consistency, all patients originally consented onto version 4.0 dated 15th April 2014 or earlier will be re-consented on to either consent form version 5.0 (08-Oct-14) or 7.0 (15-Jul-15). Acceptance of re-consent to version 7.0 participants is optional.

Patients that have had their 24 month follow up completed should not be contacted to re-consent.

Please see Appendix D: ROCSS Re-consent Decision Tree for guidance on when to consent and what data is permitted to be collected relating to the consent version used.

7.3. Randomisation by Internet and Telephone

Patients will be randomised after written informed consent has been obtained in the outpatient clinic, at pre-operative assessment or on admission for surgery.

Randomisation will be performed by a member of the ROCSS team at the site. The person undertaking randomisation or operating surgeon receiving the randomisation allocation should have no involvement in the post-operative assessment of the patient.

Patients are entered into the trial either by internet on the secure website: https://www.trials.bham.ac.uk/ROCSS or by a telephone call to the randomisation service (0800 953 0274) at the University of Birmingham Clinical Trials Unit (BCTU).

Telephone randomisation is only available Monday-Friday 0900-1700 UK time, but the secure internet-based randomisation is available 24 hours a day. These methods, which are both managed by BCTU, will ensure concealment of randomised treatment allocation. Each centre and each

randomiser will be provided with a unique log-in and password to enable them to access the online randomisation service.

Randomisation Notepads are provided in the ROCSS site file and should be used to collate the necessary information prior to randomisation. After all the necessary details have been provided, the treatment allocation will be specified and the patient will be assigned a unique trial identification number to be used on all trial related material for the patient.

The operating surgeon, assistant and theatre team will be aware of the randomised treatment allocation, but the patient and post-surgical wound assessor will remain blind to treatment allocation.

7.4. Randomisation Method

Participants will be randomised into the ROCSS trial in a 1:1 ratio of mesh reinforcement to control (standard closure without mesh). A 'minimisation' procedure using a computer-based algorithm will be used to avoid chance imbalances in important prognostic variables.

The minimisation variables will be:

1. Stoma type – ileostomy versus colostomy.
- If stoma involves an ileostomy and colostomy, it will be stratified into the colostomy group as the current literature shows that colostomies are at a higher risk of hernia than ileostomy[11].
2. Surgical incision - reopening of midline wound or stoma site only.
3. Skin closure type – primary or secondary.

8. Treatment and Follow-Up

Please see Appendix B for a detailed patient pathway for the day of surgery.

8.1. All Patients

Prophylactic antibiotics will be given to all patients according to local protocols. The ileostomy or colostomy (including bowel, fascia and skin) will be closed in accordance with the surgeon's preferred technique (i.e. stapled or hand sewn).

Immediately after closure of bowel, the size of the fascial defect should be measured before its closure. The size should be recorded as the length of the longest dimension measured. The presence of midline hernias will also be recorded, as will be whether they were repaired with separate mesh or not.

8.2. Experimental Arm – Reinforcement by Collagen Mesh

A standardised technique has been recommended by the steering committee surgeons. This has been developed and filmed and documented. In order to standardise this experimental arm, the following measures will be taken:

1. Technique DVD and instructional, illustrated paper will be distributed to the local Principal Investigator (PI).
2. A member of the Trial Management Group will offer to visit the site to assist the PI during the initial procedure. The PI should normally have performed a minimum of 20 previous stoma closures.
3. Local PIs will be asked to disseminate the technique to other participating surgeons within their hospital.
4. As further centres open, workshops will be made available to participating surgeons to review the technique.
5. Local PIs will be able to attend theatre of the trial PI during a case if they wish.

The protocol preference is for the mesh to be placed intra-peritoneally fashion (i.e. below the peritoneum). Anchoring bites will be taken in four to six sites of peritoneum (e.g. using 2-0 PDS) and the mesh will be 'parachuted' into place. Once correctly placed, the fascia above will be closed using Prolene, PDS or Nylon (surgeon preference, but excluding Vicryl). Infiltration of up to 40ml 0.25% Marcaine for infiltration into the fascial layer is recommended. The remainder of the closure will be at the surgeon's discretion.

8.3. Strattice® Mesh

Biologic meshes are sterile tissue matrices which are derived from animal tissues. The main cellular component of the tissues is removed, leaving behind a matrix upon which the patient's own tissues can grow. Since they are not formed from prosthetic material, the risk of infection when used in contaminated situations is much lower. These biologic meshes are strong, compatible with the patient's tissues and will eventually be incorporated into the patient's own tissues.

Strattice® is a popular type of biologic mesh and is in use for other indications, such as difficult abdominal wall reconstruction. It is derived from porcine dermis and once the cellular component is removed, it is packed under sterile conditions. It has already been used in parastomal hernia repair and open abdominal wall repair, but has not been used during stomas site closure as proposed by ROCSS.

The Strattice® mesh to be used within the trial is CE marked and the license includes use with abdominal wall reconstruction, hernia and hernia repair.

Indications for use

Biologic meshes (such as Strattice®) are used to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue. Indications for use include the repair of hernias and/or body wall defects. This includes its use as a bridging material to obtain closure. However its use as a prophylactic mesh to prevent hernia formation in complex and contained wounds has not been fully assessed. ROCSS provides such a model to test this type of mesh in a randomised fashion. The mesh should be prepared according to manufacturer's instructions, which include washing with saline prior to implantation.

Contraindications

This biologic mesh is derived from a porcine source and should therefore not be used in patients with known sensitivity to porcine material. Patients who object to the implantation of a porcine derived mesh may decline to consent. However, since there is no cellular component and the mesh is implanted rather than ingested, some of these patients may not object and so participation should still be offered.

8.4. The Control Arm – Established Technique

The ileostomy or colostomy will be closed in accordance with the surgeon's preferred technique, which will typically involve a handsewn or stapled bowel closure.

The non-intervention arm for fascial closure will be the preferred technique of the surgeon without mesh reinforcement. In order to provide standardisation of this arm, the following technique will be recommended:

1. The surgeon should normally have performed a minimum of 20 stoma closures.
2. The fascia should be closed with Prolene, PDS or nylon sutures; Vicryl should not be used for the fascia. This technique can include either interrupted or continuous sutures.
3. Closure of the muscle, soft tissues and skin is up to the discretion of the operating surgeon.

8.5. Compatibility with Other Studies

Patients in other colorectal cancer trials are eligible for ROCSS if the other trial does not deal with surgical technique. ROCSS would not be compatible with neo-adjuvant colorectal cancer trials such as FOxTROT. Patients where there is potential conflict should only be approached to enter the ROCSS trial after discussion with the Trial Management Group via the ROCSS Trial Office.

9. Assessment Schedule

Both the patient and the medical and nursing staff responsible for the follow-up assessments will be blinded as to whether or not the stoma closure has been reinforced with collagen mesh.

Trial data will be recorded by hospital research staff on the Case Report Forms (CRFs) and submitted to the ROCSS Trial Office at the BCTU. The patient's unique trial number, initials, hospital number and date of birth will be recorded on all proformas.

Data will be collected at patient entry, intraoperatively, 30-days post-operatively and at 12 and 24 months post randomisation. This is summarised in the table below.

	Prior to patient entry/ Day of admission for surgery	At surgery	30 days post-op +/-5 days	12 months +/- 3 m	24 months +/- 1 m
Informed consent	√				
Clinical examination	√		√	√	√
Pre-operative assessment data	√				
Operative details		√			
Clinical follow-up			√	√	√
Complications			√	√	√
Re-interventions			√	√	√
Resource usage (Cost collection)			√	√	√
Quality of Life & Pain Measures	√		√	√	√
CT scan				√	

At the time of patient entry into the trial, the following data will be collected:

- Demographics (age, gender, BMI, primary indication for stoma, when stoma was formed, diabetes, steroid medication)
- Type of stoma to be closed (ileostomy, colostomy)
- Parastomal hernia
- Incisional midline hernia from primary surgery
- Quality of life forms and pain visual analogue scale.

9.1. Treatment Evaluation

- Technique used either reinforced with collagen mesh (Strattice®) or not
- Post-operative complications (e.g. ileus, wound infection, chest infection)
- Duration of post-operative stay
- Development of hernia as judged clinically at 12 and 24 months post-randomisation
- Development of hernia as judged radiologically at 12 months post-randomisation
- Any re-operations will be recorded along with their indications (e.g. herniation, infection of mesh).
- Quality of life forms and pain visual analogue scale at 30 days post-operation, 12 months and 24 months post-randomisation.

Operative data will be recorded at time of surgery. Post-operative complications will be recorded on the 30-day Post-Operative Follow-up form.

The patients should be contacted by telephone by the research team at site prior to both of the 12 and 24 months review to remind them about their upcoming follow-up assessment and CT scan (if applicable) at 12 and 24 months. The research team at site will be provided with guidance on what should be discussed during reminder telephone calls.

At 12 and 24 months post-randomisation, Follow-up forms will be used to collect information on the presence of clinical hernia and re-intervention rates this may be done in real time or as a last resort from clinics attended within the follow up time frame (+/- windows for the visit).

A radiological assessment of the presence of hernia will be completed at 12-months post-randomisation. Quality of Life and pain forms should be completed at randomisation and then at 30 days post-operatively and 12 and 24 months post-randomisation.

10.Clinical Follow-up

10.1. Clinical Follow-Up Visits

Patients will be seen at 30 days post-op (+/- 5 days) to assess wound healing and surgical complications. Patients will then be reviewed at 12 months post-randomisation (+/- 3 months) for radiological and clinical assessment, with a final clinical assessment at 24 months post-randomisation (+/- 1 month). Any other follow-up will be at the discretion of the clinical team.

Follow-up clinical assessments will be performed by a surgeon, qualified to MRCS level or above. This should be standard practice however in cases where a MRCS level is not possible, a surgeon with MRCS equivalent or a nurse who has completed a physical examination course as part of a masters degree or similar may undertake the clinical examination.

MRCS equivalence and nurse qualification is assessed by the local PI and demonstrated by the delegation of the clinical examination duty.

Clinical examination assessors are to be blinded to the randomised allocation."

Below is the recommended standardised clinical examination technique for the closed stoma site.

Clinical examination

1. The patient should be examined according to this scheme in both standing and lying positions.

2. The patient should perform either a Valsalva manoeuvre or a forceful cough, whilst the placing of a hand over the closed stoma site.

3. You should record if the patient has:
    a. A palpable fascial defect with or without protrusion of bowel or fat;
    b. A global weakness around the stoma scar, without palpable fascial defect.

4. If in doubt, a second blinded clinician should be consulted and consensus achieved.

Definition of a hernia

For this study, a clinical hernia is defined as a palpable or visible discrete protrusion at the site of the stoma closure, possibly with a palpable fascial defect. A clinically global weakness is defined as a palpable or visible generalised weakness/ protrusion, which takes on no discreet nature and where no

fascial defect is palpable. A radiological hernia is defined as any breach in the abdominal wall muscles or fascia visible on CT scan, with or without the passage of bowel, omentum or fat through it.

This study will include optional consent to allow future linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. CPRD, THIN, QResearch), secondary care data (Hospital Episode Statistics; HES) and mortality data from the Office of National Statistics (ONS) through The Health and Social Care Information Centre and other central UK NHS bodies. The consent will also allow access to other new central UK NHS databases that will appear in the future. This will allow us to extend the follow-up of patients in the trial and collect long-term outcome and health resource usage data without needing further contact with the study participants. This is important as it will link a trial of a treatment that may become a clinical standard of care to long-term outcomes that are routinely collected in clinical data, but which will not be collected during the follow-up period of the trial.

10.2. Twelve Month Post-Operative CT Scan

One of the secondary outcome measures in ROCSS is the presence of a hernia on CT scan at 12 months post randomisation. For these purposes, a hernia will be defined as any evidence of a defect present in the abdominal wall (see above: Definition of a hernia). A time frame of +/- 3 months from this 12 month time point is acceptable.

It is expected that the majority of trial participants will have had a stoma for colorectal cancer. In this group of patients, a one year post-operative abdominal/pelvic CT scan to assess for cancer recurrence is routine in the UK. This CT scan will be performed as a standard CT scan of the abdomen and pelvis as per the participating hospital's local protocol using a maximum slice thickness of 5mm. This routine scan will be used to assess for hernia recurrence instead of arranging a study one-year post-randomisation scan. In exceptional cases, an MRI scan as per participant's hospital local protocol may also be used to assess for hernia recurrence for patients undergoing surgery for cancer.

Non-cancer patients who have a stoma for a benign condition (such as Crohn's disease) usually do not routinely require CT follow up. These patients thus need an additional CT scan at one year to assess for hernia recurrence. This CT can be performed in one of the following two ways:

1. **Standard low dose CT KUB protocol**: (to detect renal tract calculi) using no oral contrast, no IV contrast and a maximum slice thickness of 5mm, so enabling a lower radiation dose exposure.
2. **Limited CT scan protocol**: For those patients who are having a CT scan that would not normally be performed (i.e. a stoma originally placed for benign disease) a local centre may choose to follow a low radiation dose protocol. This should be performed as follows:
    i. No IV or oral contrast is required.
    ii. Instead patient drinks 1L of water over 45 minutes (flavoured if desired).
    iii. Low dose scan (same as the local institution's CT-KUB protocol).
    iv. Stoma site identified visually on the skin and a marker placed (e.g. a thin paper clip).
    v. Scout scan of abdomen performed.
    vi. This is used to plan the axial slices in which a block 10cm above and 10cm below the skin marker (but no lower than pubic symphysis) is acquired. This is to take into account that the skin closure site may not correspond to the abdominal muscle closure site, particularly in obese trial participants).
    vii. The skin marker is removed (in order to avoid streak artifact).

viii. The planned axial slices are acquired.

ix. The images are reviewed by the CT radiographer. They may choose to extend the acquisition to include areas of interest in the abdominal wall not fully included on the scan.

A named local radiologist will be involved at each site to provide local reports which maintain local clinician blinding to placement of mesh.

CT scans will be performed at local centres and then centralised for review by two blinded radiologists. The scans will be transferred either by electronic systems if available or by a compact disc to the BCTU. The radiologists will use a standardised CRF to review the CT scans. No direct involvement is required from radiologists at local centres. The local PI and registrar teams will organise the scans. Transfer will be organised with the help of local radiologists.

10.3. Ultrasound Sub-study

One of the secondary outcome measures in this study is to evaluate the detection rate of stoma site hernias with a CT scan at one year. This CT is performed as a 'standard' scan, in a supine position with the patient holding their breath. It is possible that this CT scan will not detect abdominal wall hernia owing to the lack of a 'dynamic' element. In order to address this concern, we propose using ultrasound to scan 40 consecutive patients who have undergone their one year follow-up CT scan in the Queen Elizabeth Hospital Birmingham as part of the ROCSS trial.

This sub-study is described in detail in the sub-study protocol that can be found in the appendices.

10.4. Pilot Patient Incentive Scheme

A pilot scheme is to be introduced to a number of sites in the UK to see if patient incentives improve uptake of 24 month follow up visits in those patients that have not withdrawn from the study but failed to attend after the initial invitation.

- Patients that have failed to attend their initial 24 month follow up visit will be offered a small gratuity in the form of a gift card for twenty pounds when re-arranging their 24 month follow up. Sites will be provided with a complimentary slip that they may use for patients to offer this gratuity.
- This offer of a gratuity will be given to patients at attendance of their 24 month follow up assessment.

Patients will not be offered any form of payment at initial contact discussing the upcoming 24 month follow up assessment nor given to those patients who attend their 24 month follow up after initial invitation.

10.5. Patient Withdrawal

Patients may withdraw from the trial at any point. Within ROCSS there are different types of withdrawal, if a patient decides to withdraw the details should be documented in the medical notes and the ROCSS trial office informed.

The types of withdrawal in ROCSS are:

- Withdrawal from trial-specific follow-up: the patient has had trial treatment but does not wish to be followed up according to the protocol. The patient will be followed up according to standard practice. It must be confirmed that the patient has agreed that follow-up data collected at standard clinic visits may be used in the final analysis.
- Total withdrawal from the trial: the patient is not willing to be followed up for trial purposes at any further visits, i.e. only data collected prior to the withdrawal of consent can be used in the final analysis.

All patients are analysed on an Intention-To-Treat basis, therefore all patients are followed within the trial, regardless of receipt of randomised allocation, unless the patient withdraws consent.

10.6. Unblinding of patients

Patients will be asked to complete a "Patient Allocation Request" form providing consent for the ROCSS study office to directly send the patient their randomisation allocation. Patients wishing to be notified of their randomisation prior to completing the study may do so by written request directly to the ROCSS team at BCTU.

By the ROCSS study office corresponding directly with the patient, it will ensure that sites remain blind to randomisation allocations.

The Patient Allocation Request form will be completed at the patient's next follow up appointment or sent a letter via post.

In ROCSS-EX, this process is streamlined for patients. If they request to be informed of their allocation during the telephone consultation, they will be asked to provide contact information (email or postal address), which will be submitted to the trial office along with the follow-up data. Once the data collection period has ended and the database has been locked, the patients who have requested to be told their randomised allocation will be informed.

10.7. Compliance with the Protocol

The investigators and sponsor will agree to implement the study protocol as written. The study will be performed in accordance with the Declaration of Helsinki, International Committee on Harmonisation of Good Clinical Practice Guidelines and the local laws and recommendations recommended by the European Community.

10.8. End of Trial

The end of the trial for regulatory purposes is defined as 6 months after the date of the last clinical follow-up appointment of the last patient undergoing protocol based treatment.

10.9. Trial Extension

The main results from ROCSS have now been published[15]. The results indicate a significant reduction in the rate of incisional hernia after reinforcement of the stoma closure site with biological mesh. However, they do not show a benefit to the patient in terms of quality of life or to the NHS in cost.

A 5-8 year follow-up will take place to investigate these outcomes and is described fully in Section 19.

11.Recruitment

11.1. Projected Recruitment Schedule

One of the main aims of the feasibility study was to assess the ability to recruit patients into the trial. The feasibility study aimed to recruit 90 patients over 12 months. This was achieved ahead of schedule and we have now continued into the main phase III trial, where the aim is to randomise a further 470 patients to a total of 560 patients. The recruitment projection is that this will take 2.5 years in total. We are aiming to recruit patients from at least 30 units across the United Kingdom.

The projected recruitment is:

- Feasibility Study: 90 patients
  - Months 1-12: 5 centres at rate of 1 patient/ month for 12 months = 60 patients
  - Months 6-12: 5 additional centres at rate of 1 patient/ month for 6 months = 30 patients

- Phase III trial: 470 patients
  - Months 12-30: 10 centres at rate of 1 patients/ month for 18 months = 180 patients (note: these will be centres from the feasibility study)
  - Months 12-30: 10 further centres at rate of 1 patient/ month for 18 months = 180 patients
  - Months 18-30: 10 new centres at rate of 1 patient/ month for 12 months = 120 patients
- If recruitment is ahead of target, the sample size of the phase III study will be increased to 790, which would provide 90% power to detect a 40% reduction in 2 year clinical hernia rate.

11.2. Screening Logs

As part of ROCSS, a screening log of potentially eligible patients will be kept by all participating centres.

Screening logs should be kept of those patients who are potentially eligible for entry into the trial i.e. those patients undergoing stoma reversal, but who are subsequently not randomised, missed or refuse randomisation. The reason for non-inclusion should also be documented.

A recruitment contact at site should be nominated; the ROCSS Study Office will request this information on a monthly basis.

12.Safety Monitoring Procedures

12.1. Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence which:

- Is fatal or immediately life-threatening (the patient was at risk of death at the time of the event). This does not refer to an event that hypothetically might have caused death if more severe.
- Requires or prolongs hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a newly identified cancer.

Stoma site closure specific SAEs include, but are not limited to:

- Unexpected events occurring during the surgical intervention e.g. excess wound infection, excess wound breakdown, abscesses associated with the mesh.
- Postoperative pain above that normally expected following the surgical intervention.

Note that within ROCSS, hospitalisation for elective surgery is NOT considered to be an SAE.

12.2. Recording and Reporting Serious Adverse Events

The Investigator must report in detail all SAEs believed to be due to surgery or the use of the biological mesh.

SAE recording shall begin as soon as the patient signs the Patient Consent Form. All SAEs will be collected for all patients in the study and must be recorded on the SAE form and faxed to the BCTU on 0121 415 8871 as soon as site staff become aware of the event.

Details recorded for each Adverse Event will include:

- nature of the sign or symptom
- date of onset
- date of resolution (duration)
- the severity
- the relationship to study treatment or other therapy

- the action taken (if any)
- the outcome

SAEs still present at the end of the study must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the patient's study participation is complete and, when appropriate, until the end of the planned follow-up period of the study.

12.3. Timeframe for reporting SAEs

Any event that satisfies the SAE reporting criteria/ are to be reported for all patients in the study from trial entry to the 30 days post-operative review .. After this 30 days post-operative time point and until the completion of the 24 month follow up only events satisfying the SAE reporting criteria **and** pertaining to the abdomen should be reported.

12.4. Responsibilities for Reporting of SAEs

The BCTU will report all SAEs to the DMEC at regular intervals (at least annually), and to the main REC annually. Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations.

13.Sample Size, Statistics and Data Monitoring

13.1. Sample Size

Current data (as identified through a systematic review of the published literature) is heterogenous due to reports from diverse study populations with incomplete follow-up. Many studies showed low herniation rates due to no clinical follow-up, where they were based on patient reports.

The sample size calculation was therefore based upon studies with active follow-up where hernia was a primary endpoint, which showed higher hernia and re-operation rates[2-4]. In these studies, the clinically detectable hernia rate was over 25%. To detect a 40% reduction in 2 year clinical hernia rate (i.e. from 25% to 15% with the biological mesh) requires 500 patients (250 in each arm, with 80% power, alpha=0.05). This was increased to 560 patients (280 per arm) to allow for a 10% drop-out rate. Prophylactic mesh placement for other types of hernia (such as parastomal hernias) has shown reductions of between 40-100%[12 13 16], so this reduction sits at the cautious end of the range.

As recruitment is ahead of target, the power of the study may be increased to 90% with 15% drop-out (rather than 10%, to also account for patients who won't contribute to the primary outcome as they have not had their stoma reversed). To detect a 40% reduction in 2 year clinical hernia rate with 90% power requires 670 patients, increasing to 790 patients (395 per arm) to allow for a 15% drop-out rate. There will be an ongoing review of recruitment, sample size assumptions and dropout rates by the DMEC which will guide the TMG as to whether continuing recruitment to 90% power is feasible.

In May 2015 the recruitment target of 670 was met and the sample size was increased to 790 patients. Recruitment extended for 6 months, until November 2015.

13.2. Statistical Data Analysis

The primary outcome measure is the clinical hernia rate at 2 years. The number of clinical hernias at 2 years in the two treatment groups (biological mesh and control) will be compared using a chi-squared test. Treatment effects will be expressed as a relative risk with 95% confidence interval. Any categorical secondary outcome measures (e.g. radiological hernia rate, re-operation rate, infection rates) will be analysed in the same way as the primary outcome. Continuous data (e.g. EuroQoL EQ-5D, pain scores) will be analysed using an independent 2-sample t-test (or the non-parametric equivalent as appropriate) at each time point, with the 2 year data considered the main analysis time point. Since data is being collected over multiple time points, longitudinal plots of the continuous data

will be produced for visual presentation of the data, and a repeated measures analysis will be performed across all time points.

All analyses will be intention to treat, whereby patients will be analysed according to the treatment group to which they were randomised regardless of whether they complied with this treatment. All p-values will be 2-tailed and a p-value of <0.05 will be considered statistically significant.

The only planned subgroup analyses with be to compare the effect of biological mesh depending on stoma site (ileostomy or colostomy); surgical incision (reopening of midline wound or stoma site only); and skin closure type (primary or secondary). Subgroup analyses will employ a test of interaction to explore whether there is evidence that the treatment effects differ across subgroups. As with all subgroups analyses these will be interpreted with caution, and will be considered hypothesis generating.

13.3. Exploratory Data Analysis

An exploratory analysis will compare the radiological hernia rate at 1 year with clinical hernia rate at 2 years. This will provide useful information on the value of using a CT scan as an early diagnostic tool of herniation, which could then be used in future abdominal wall studies as a surrogate endpoint for clinical hernia. Correlation between CT and clinical hernia rates will be calculated as follows:

- The proportion of false negatives – i.e. clinical but not radiological hernias
- The proportion of false positive – i.e. radiological but not clinical hernias (at 2 years)

An additional analysis will correlate patient reported symptoms at the closed stoma site to clinical examination and CT findings.

14.Data Monitoring

14.1. Data Monitoring and Ethics Committee

During the study, interim analyses of safety and outcome data will be supplied, in strict confidence, to an independent DMEC along with any other analyses that the committee may request.

The DMEC will meet once the first 90 patients have been entered into the study or at the end of the 12 month feasibility part whichever occurs first to assess the safety data, and advise on continuation to the main phase III trial. Since this is an internal feasibility study, and this safety data will be included in the main analysis of the ROCSS trial, this data will remain confidential, except to members of the DMEC.

During the main phase III trial, the DMEC will meet annually, or more frequently if considered appropriate, and will advise the chair of the Trial Steering Committee if, in their view, the randomised comparison in ROCSS has provided both (a) “proof beyond reasonable doubt” that for all, or for some types of patient, treatment with the collagen mesh is clearly indicated or clearly contraindicated in terms of a net difference in the main outcome measures, and (b) evidence that might reasonably be expected to influence the patient management by many clinicians.

The Trial Steering Committee can then decide whether to modify the study protocol. Unless this happens, however, the steering committee, the collaborators and all of the central administrative staff (except the trial statisticians who supply the confidential analyses) will remain ignorant of the interim results.

If the clinical coordinators are unable to resolve any concerns satisfactorily, collaborators, and all others associated with the study, may write through the ROCSS trial office to the chair of the DMEC,

drawing attention to any worries they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

15. Health economics analysis

In general terms, the aim of the economic evaluation is to determine the cost-effectiveness of using a collagen tissue matrix compared to standard closure techniques for patients undergoing elective closures of stomas, and to establish the lifetime cost and outcomes associated with either collagen tissue matrix or usual closure of stoma sites.

The health economic analysis has two distinct parts. The first part is a cost-effectiveness analysis conducted alongside the randomised clinical trial. The second part is a model-based cost-effectiveness analysis building on the trial-based analysis and using published data on long-term outcomes and costs. Although the trial-based analysis is important in determining costs, quality of life, and cost-effectiveness over the first two years after the intervention, the model-based analysis will provide the most useful information to decision makers in estimating the long-term impact on costs and patient outcomes.

15.1. Trial-based cost-effectiveness analysis

The base-case economic evaluation to be conducted alongside the randomised clinical trial will estimate the relative cost-effectiveness of using a collagen tissue matrix compared to standard closure techniques for patients undergoing elective closures of stomas (ileostomy or colostomy). The primary within-trial cost-effectiveness analysis will estimate the cost per hernia clinically detected and cost per additional quality adjusted life (QALY) year gained, both over a two-year period, matching the time point for the primary clinical outcome. The base-case cost-utility analysis will estimate the cost per additional quality adjusted life (QALY) year gained using data from the full 12 month follow-up. Cost and outcome data will be collected on every patient within the trial.

15.1.1. Cost data

Data will be collected using a short questionnaire from a representative sample of hospitals to ensure generalizability. Data on resource use associated with each strategy will be collected and will include information on supplies (collagen mesh), length of pre and post-operative hospital stay, drugs, time(days) to return to normal activities, length of hospital stay due to adverse effects, equipment and staff involved in pathways for each strategy. Unit costs for supplies, inpatient stays, drugs, equipment and staff will be collected from published sources such as the National Health Service (NHS) Schedule of Reference Costs, Unit Costs of Health and Social Care (PSSRU), British National Formulary (BNF) and local estimates where possible.

15.1.2. Outcome data

Outcome data from the trial will be the incidence of clinically detectable closure site hernias at 2-years. EQ-5D data will be collected from each patient at baseline (pre-operation), at 30 days post-operation and at 12 and 24 months post-randomisation in order that QALYs can be calculated using the UK tariff (Dolan, 1997)

15.1.3. Analysis

A cost-consequences analysis will initially be undertaken. This will detail all costs and outcomes for 30 days post-operative, 12 months and 24 months follow-up. For each trial arm, mean costs and outcomes and their 95% confidence intervals will be presented. An incremental cost-effectiveness analysis will be undertaken from an NHS perspective to determine the cost per hernia clinically detected and cost per additional quality adjusted life (QALY) year gained, both over a two-year period. Incremental cost effectiveness ratios (ICERs) will be estimated by dividing the difference in mean cost between two treatments by the difference in mean outcomes.

Non-parametric bootstrapping will be used to illustrate and quantify uncertainty. 5000 paired estimates of mean differential costs and outcomes will be estimated and presented graphically on a cost-effectiveness plane. To determine the probability of a treatment being deemed cost-effective compared to an alternative treatment, cost-effectiveness acceptability curves (CEAC) will be constructed. This shows the probability that an intervention is cost-effective, relative to the chosen comparator, across a range of values that represent a decision makers' willingness to pay for an additional unit of outcome.

The base-case analyses to be conducted are:

- Cost per hernia clinically detected and cost per additional quality adjusted life (QALY) year gained, both over a two-year period
- Cost per QALY gained at 12 months

15.1.4. Sensitivity analysis

Sensitivity analysis will test the robustness of the results. Key parameters will be varied to determine the impact of changes on results. Non-parametric bootstrapping and probabilistic sensitivity analysis will be undertaken to explore uncertainty in the confidence to be placed on the results of the economic analysis and cost-effectiveness acceptability curves presented.

Pre-specified sensitivity analyses are as follows:

- Cost per hernia clinically detected at 2 years
- Cost per additional quality adjusted life (QALY) year gained at 2 years
- Alternative costs of the intervention

Data (costs and effects) will be analysed as:

- Complete case analysis, where only participants with complete data are included. This will be the base case analysis.
- multiple imputation, where all study participants are included (imputed values will be used for missing costs and effects)

15.2. Model-based cost-effectiveness analysis

The model-based economic evaluation will estimate the long-term cost-effectiveness of using collagen tissue matrix for patients undergoing elective closures of stomas. It is anticipated a mathematical model will be constructed to determine the long-term (beyond 24 months) costs and outcomes associated with either collagen tissue matrix or usual closure of stoma sites. The model will be developed using TreeAge Pro Suite 2015 software (TreeAge Software Inc, Williamstown, MA, USA).

The model structure will be informed by reviewing modelling studies that have been undertaken which consider long-term outcomes associated with incision hernias or outcomes after stoma closures and by expert opinion within the team. Costs in the model will include those for the collagen tissue matrix pathway and usual closure techniques derived from the trial-based analysis, re-admissions, re-operations and long-term hernia. Outcomes will be in the form of survival and quality of life (if available) and will use data collected from the trial and literature on quality of life after a hernia/stoma.

The model will be run over remaining lifetime, with costs and benefits discounted at a rate of 3.5%. The incremental cost-utility analysis will be conducted from an NHS and Personal Social Services (PSS) perspective. Extensive deterministic sensitivity analysis will be undertaken to assess the impact of changing the values of key parameters. For each important model parameter, we will determine a point estimate and construct a probability distribution around the estimate. Probabilistic sensitivity analyses will be conducted to deal with uncertainty in model parameters and cost-acceptability curves presented.

16.Organisation

To ensure the smooth running of ROCSS and to minimise the overall procedural workload, it is proposed that each centre should designate individuals who would be chiefly responsible for local coordination of the surgical and administrative aspects of ROCSS. The ROCSS Trial Office will provide as much assistance as they can to local co-ordinators and investigators in obtaining Trust approval in each centre and helping resolve any local problems that may be encountered.

16.1. Funding

The ROCSS feasibility study was funded by an unconditional educational grant from LifeCell.

Follow-up and analysis of the phase II trial has been funded by the NIHR Research for Patient Benefit Programme.

The study has been adopted to the NIHR Clinical Research Network portfolio. This will have benefits in coordination of research efforts, dissemination of trial information and local support for investigators.

16.2. Principal Investigator at each Centre

Each ROCSS centre should nominate a Consultant Colorectal Surgeon to act as the local Principal Investigator (PI) and bear responsibility for the conduct of research at their centre. The responsibilities of the local PI will be to ensure that all medical and nursing staff involved in the care of potential patients are well informed about the trial and trained in trial procedures, including obtaining informed consent. Close collaboration between all clinical teams is particularly important in order that patients for whom the ROCSS trial is an option can be identified sufficiently early for entry into the trial.

The local PI will also be responsible for ensuring standardisation of the technique for reinforcement with the collagen mesh. The local PI should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

16.3. Radiologist at each Centre

It is suggested that each ROCSS centre should nominate a Consultant Radiologist as Local Radiology Coordinator. This person will be responsible for ensuring that the 12-month CT scan is carried out to protocol for all ROCSS patients when requested to do so by local clinicians and to provide these scans for centralised study evaluation. The nominated radiologist will be sent updates and newsletters and will be invited to ROCSS progress and training meetings.

16.4. Central Coordination

The Trial Office at the BCTU is responsible for providing the following trial materials:

- The Site File, including all regulatory documentation required to define the involvement of the centre in the trial and printed patient materials, such as participant information sheets, consent forms and GP letters.
- An online randomisation system, including individual log-in and passwords and guidance will be supplied to each collaborating centre, after relevant authorisations have been obtained.

Additional supplies of any printed material can be obtained on request. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data and for reporting of serious adverse events to the sponsor and regulatory authorities on behalf of the Chief Investigator and for any interim and final data analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

16.5. Clinical Queries

During office hours, the clinical coordinators (see inside front cover for contact details) provide an on-call service for any clinical queries about the trial.

16.6. Strattice® Collagen Mesh Supply

The Strattice® collagen mesh to be used within the trial will be provided free of charge from Lifecell. Only one collagen mesh per patient randomised to receive it will be supplied free of charge. One dedicated mesh will be delivered to each site upon opening. When this mesh has been used, a re-order form can be faxed to LifeCell who will re-supply within 24 hours for orders placed Monday – Thursday.

16.7. CT scans

For the main phase of the trial, hospital trusts will be reimbursed for the follow-up CT scan performed at 12-months post-randomisation for those patients who would not normally undergo a scan at this time (ie colorectal cancer patients in the UK who would normally have a CT scan at one year would not be reimbursed for the cost of this scan). Reimbursement will be via an invoice to the ROCSS Study Office. Detailed information about pathways for sending CT scans back to the central office for interpretation will be provided on a site by site basis by the ROCSS Study Office. For hospitals with PACS links, there will be provision for anonymised electronic transfer. For centres without these links, there will be provision for secure postage of a CD back to the ROCSS Trial Office at the BCTU.

Inclusion of patients in the ROCSS trial should therefore incur only minimal additional costs for participating hospitals. Follow-up appointments can be co-ordinated to fit in with the patient's existing follow-up schedule.

16.8. Patient and Public Involvement

IA (the ileostomy and internal pouch support group) is a UK registered charity whose primary aim is to help people who have to undergo surgery that involves the removal of their colon (known as a colectomy) and the creation of either an ileostomy or an ileo-anal pouch (http://www.iasupport.org/). It was started in 1956 by a group of people who had ileostomies themselves, together with some members of the medical profession. It was the first ostomy association in the United Kingdom and it is a registered national charity (no. 234472).

The IA has 55 local groups throughout Great Britain and Ireland and represents the widest possible representation of our sample group for adequate Patient and Public Involvement. At an early stage, the protocol was submitted to the IA's research sub-committee for feedback and approval. After some minor changes, particularly to the patient information sheet, the National Secretary of the IA confirmed their support for the trial and protocol.

16.9. Publication and Dissemination of Results

A meeting will be held at the end of the trial to allow discussion of the main results among the collaborators prior to publication. The success of the trial depends entirely on the wholehearted collaboration of a large number of doctors, nurses and researchers. For this reason, chief credit for the main results will be given not to the committees or central organisers, but to all those who have collaborated in the trial. A writing committee will be convened to produce publications on behalf of the trial collaborators. Centres will not be permitted to publish data obtained from participants in the ROCSS trial that uses trial outcome measures without discussion with the Chief Investigator and the Trial Steering Committee.

It is envisaged that the results from the ROCSS trial will be:

- Used to make recommendations to commissioners about the routine use of prophylactic reinforcement of closure of stoma sites, through the Nice Institute of Clinical Excellence (NICE) guideline structure
- Reported to the Ileostomy Association in order to inform their members and for dissemination to the general public
- Published in a peer reviewed, high impact surgical journal
- Presented at regional, national and international conferences

17.Research Governance

The conduct of the trial will be in accordance with the principles of the International Committee on Harmonisation of Good Clinical Practice Guidelines and the Research Governance Framework for Health and Social Care plus any subsequent amendments.

17.1. Sponsor

National sponsorship will be provided by the University of Birmingham upon signing of the Clinical Study Site Agreement with each trial site.

17.2. Clinical Trials Unit

Data from this trial will be handled by the BCTU at the University of Birmingham. BCTU is a full-time research facility dedicated to, and with substantial experience in, the design and conduct of randomised clinical trials. The BCTU recognises the responsibilities of a data management centre with respect to the ethical practice of research and the adequate protection of human subjects.

17.3. Confidentiality of Personal Data

The trial will collect personal data about participants, and medical records will be reviewed for all patients and routine physical examinations will be performed. Participants will be informed that their trial data and information will be securely stored at the trial office at the BCTU, and will be asked to consent to this. The BCTU abides by the UK law Data Protection Act 2018. The data will be stored on a secure computer database, and all personal information obtained for the study will be held securely and treated as strictly confidential. Any data processed outside of the BCTU will be anonymised.

17.4. Long-Term Storage of Data

In line with Good Clinical Practice guidelines, all essential documentation and data will be retained for at least 10 years.

17.5. Indemnity

ROCSS was developed by the West Midlands Research Collaborative and the BCTU, and the feasibility study is being supported by Lifecell. The University of Birmingham is the trial 'sponsor.' The normal NHS indemnity liability arrangements for clinician-initiated research will, therefore, operate – see NHS Executive Health Service Guidelines HSG (96) 48, 8th November 1996. It should be noted, however, that negligent liability remains the responsibility of the hospital, whether or not a patient is part of a clinical trial, because of the duty of care that the hospital has for their patients.

18.Results from the ROCSS trial

The ROCSS trial was published in *The Lancet* in February 2020[15]. Of 1,286 patients screened, 790 were randomised, 394 to mesh closure and 396 to standard closure. The clinically detectable hernia rate at 2 years was significantly lower in the mesh group (12% vs 20%, RR 0.62, 95% CI 0.43 - 0.90, p=0.012). At 1-year there was a lower incidence of radiological hernia in those receiving mesh compared to standard treatment (RR 0.42, 95%CI 0.26 – 0.69, p<.001). Despite this, no benefit was seen in the rates of symptomatic hernia, surgical reintervention, wound infection, seroma, quality of life, pain scores or serious adverse events.

To investigate the long-term impact of mesh use in stoma closure on quality of life and cost effectiveness ROCSS - Extended Follow-up (ROCSS-EX) has been funded by the NIHR RfPB.

19.ROCSS-Extended Follow-up (ROCSS-EX)

19.1. Research Question

Is there a significant improvement in long-term quality of life for patients that have a biological mesh reinforcement of the abdominal wall at the time of closure of stoma site, and is the intervention cost-effective?

19.2. Aims

1. To investigate if the biological mesh closure group has a significant long-term improvement in participant quality of life 5-8 years after stoma reversal.

2. To determine if the intervention is cost-effective after 5-8 years.

19.3. Objectives

- To assess the long-term effects of mesh reinforcement of the abdominal wall at the time of stoma closure on quality of life
- To assess the participant reported incisional hernia rate
- To report the number of hernia related hospital visits
- To report the number of interventional procedures related to the stoma closure site or any subsequent hernia
- To explore the long-term cost effectiveness of mesh reinforcement

19.4. Outcome measures

Primary:

Quality of life at 5 to 8 years following closure of stoma site comparing participants who had mesh reinforcement of their abdominal wall with participants that had a standard closure. This will be assessed using the HerQLes tool[17,18].

Secondary: (all at 5-8 years follow-up)

- Participant reported incisional hernia rate
- Number of hospital visits for any hernia related reason
- Number of interventional procedures related to the stoma closure site or hernia
- Longitudinal QoL assessed using EQ-5D
- Cost analysis for all additional hernia related events

19.5. Inclusion criteria

All participants included in ROCSS are eligible to be included in ROCSS-EX unless they withdrew or did not have their stoma reversed during the duration of the original trial. For those participants who have died, only routinely collected data will be used.

19.6. Sites

All of the UK sites from the original ROCSS trial will be eligible to participate in ROCSS-EX. The two international sites will not participate in ROCSS-EX.

19.7. Choice of QoL measures

A hernia-related quality of life measure will be included to provide more hernia specific information that will allow a better measure of the impact both to the patient and also to inform the cost-effectiveness analysis. The HerQLes tool was specifically designed to evaluate QoL in patients undergoing abdominal wall repair[17,18], such as a stoma closure. It contains 12 items, and can be used

both before and after surgery, focusing on abdominal wall function. Each of the 12 questions relate to the patient's abdominal wall function which means that it will be relevant to patients with and without a hernia (such as the ROCSS participant population). It will therefore be possible to use the same tool in both groups i.e. those who had mesh at the time of stoma closure and those who did not, and for participants with and without a hernia.

The HerQLes quality of life survey was not available when ROCSS was developed and so was not used for the original trial. Therefore, we do not have before and after scores to compare. However, the scores can be compared across groups of participants and it is known (from the original ROCSS data and our follow-up data) whether participants have had mesh inserted at the time of stoma closure and whether or not they have or have had a hernia. These groups will provide us with various comparisons to make and so the following exploratory analyses will be investigated limited to the primary outcome;

- Comparison within the control group (no mesh) for those who have developed a clinical or radiological hernia during the follow up period to those without a hernia. This will show the effect that having an incisional hernia has on a participant's quality of life.
- Comparison between the control group and the mesh group for those who did not develop a clinical or radiological hernia during the follow up period. This will show us if inserting a mesh in itself has any effect on quality of life. This has become an even more important comparison with the recent concern regarding mesh use.
- Comparison between the control group and the mesh group for those who have gone onto develop a clinical or radiological hernia. This will show us if developing a hernia despite having a prophylactic mesh inserted has a different effect on quality of life.

The ROCSS trial originally used a non-specific QoL measure (EQ-5D). This will be repeated but evaluated as a secondary endpoint to look at longitudinal impact and provide QALY data.

19.8. Consent

The consent obtained for the original ROCSS trial does not specifically include contact to complete longer-term follow-up. Therefore, participants will be contracted by letter to inform them about ROCSS-EX. Re-confirmation of consent and agreement to continue participation will be obtained during the telephone consultation and documented in the participant's medical records (electronic or paper).

19.8.1. Contacting participants

Each site holds an identification log in the local site file that lists the participants recruited to the original ROCSS trial. This information will also be available to sites within the ROCSS-EX database, limited to only participants from the site and that are eligible for follow-up within ROCSS-EX. Sites will then establish whether each participant is alive according to the hospital records.

Prior to contacting living participants by telephone, the site will send them the ROCSS-EX Participant letter, which briefly explains;

- the nature and purpose of the follow-up
- the local team will contact the participant by telephone at least two weeks later to undertake the follow-up, or arrange a time that is convenient for them to complete it
- how they can indicate they do wish to opt out of the additional follow-up by telephone; telling the local team member when they call, or contacting the local team beforehand by either post, telephone or email, or the Trial office at BCTU by email

A Participant Information Sheet specific to ROCSS-EX that provides more detailed information and explanation will be sent with the letter.

19.8.2. Uncontactable patients

For participants that have died or otherwise cannot be contacted, data will be collected from the medical records where consent was given as part of the original ROCSS trial to the use of routinely collected data for long-term follow-up.

19.9. Blinding

Local teams at site will remain unaware of the treatment allocations participants received (blinded).

In ROCSS, participants were also blind to the treatment allocation. For either clinical reasons or at a participant's request approximately 100 participants been informed of the allocation received (unblinded). The ROCSS-EX Participant Information Sheet explains to participants the importance on maintaining blinding of staff at sites. Site staff will be asked to confirm if they are blind to the allocation when follow-up data is collected. It is possible that unblinding of site staff may be unavoidable in some instances – the allocation may be recorded in the medical records so the review cannot be completed without unintentionally unblinding the reviewer, or a participant may mention it during the telephone consultation. Site staff will be asked to confirm whether they are blind to the allocation, and if not to account for this.

19.10. Data Collection

ROCSS-EX will collect data from trial entry into the original ROCSS trial until the date the ROCSS-EX follow-up is completed.

Data will be collected from two sources:

- The first is routinely collected electronic health records (or paper records if electronic records are unavailable) that local collaborators will access. This will include the number of hospital admissions related to either the stoma site or abdominal symptoms, the number of interventions in relation to symptoms and pathology at the stoma closure site.
- The second source of data will be the participant. Telephone interviews will collect participant reported information including the use the EQ-5D-5L and HerQLes tool. A standardised telephone script has been developed for collaborators to use during the telephone call.

The data gathered will be uploaded directly into a secure ROCSS-EX REDCap database hosted at the University of Birmingham by the local team. Worksheets to aid the collation may be used prior to upload. All local collaborators will receive trial specific training that will include the delivery of the telephone follow-up.

19.10.1. Case Report Form (CRF) Completion

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to the ROCSS-EX guide on CRF completion.

For the ROCSS-EX, CRFs will be an electronic record completed at site, only by those at site delegated the task of doing so. Forms will be considered "complete" once all data fields have been either completed unambiguously or it has been made explicit that the data is unobtainable.

In all cases it remains the responsibility of the site's PI to ensure that the CRF has been completed correctly and that the data are accurate.

19.10.2. 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 will be accessible and maintained.

Data	Source
Participant Reported Outcomes (EQ-5D-5L and HerQLes)	The interview administration EQ-5D-5L and HerQLes is the source, obtained by interview directly with the participant for transcription onto the CRF, in which case the CRF is source data.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source documents. Information will be transcribed onto CRFs.
Health Economics data	Obtained by (1) interview directly with the participant for transcription onto the CRF in which case the CRF is source data. (2) To the medical record in which case the original clinical annotation is the source document. Information will be transcribed onto CRFs.
Drop out	Where a participant expresses a wish to withdraw, the conversation must be recorded in the medical records.

19.11. Statistical Analysis

Power calculation

There were 790 participants randomised in the ROCSS trial (394 in Mesh arm, 396 in No Mesh arm). Of these, 98 participants (49 in Mesh arm, 49 in No Mesh arm) have either died, did not have the stoma reversed, withdrew from the trial or were recruited from international sites. Accounting for these, 692 participants (345 in Mesh arm, 347 in No Mesh arm) remain that can be approached. Allowing for 15% dropout, it is anticipated data at 5-8 years follow-up will be obtained for approximately 588 participants (293 in Mesh arm, 295 in No Mesh arm).

The primary outcome for this study is the HerQLes quality of life score. With 588 participants expected to provide data for this, there will be over 85% power to detect an effect size of 0.25 standard deviations (two-sided alpha of 0.05). To detect a difference of 0.3 standard deviations (two-sided alpha of 0.05), with 588 participants there will be over 95% power.

Analysis methods

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

All analyses (primary and secondary outcomes) will be by intention-to-treat (ITT). All estimates of differences between groups will be presented with two-sided 95% confidence intervals, unless otherwise stated. P-values will be reported from two-sided tests at the 5% significance level.

The data for the primary outcome is continuous and therefore will be summarised using the mean and standard deviation along with minimum and maximum values with respect to the intervention arms and overall. The primary outcome will be analysed using a linear regression model and an adjusted mean difference and 95% confidence interval will be estimated from the model.

The secondary outcomes consist of continuous, binary and count data types. For all secondary outcomes that are continuous in nature, they will be analysed using the same statistical method as described for primary outcome.

For those secondary outcomes that are binary in nature, data will be summarised as number and percentage of participants in each category by intervention arm. An adjusted relative risk and 95% confidence interval will be estimated from a log-binomial regression model. For those secondary outcomes that are count data type, these will be analysed using a Poisson regression model (or negative binomial regression if there is evidence of overdispersion) with an offset for the length of time the participant was in the trial included in the model, to obtain an adjusted incidence rate ratio (IRR) and 95% confidence interval.

19.12. Health Economic analysis

The economic evaluation will assess the differences in healthcare costs and participant quality of life in the two trial arms. An economic evaluation is a comparative analysis of two or more interventions in terms of their costs and consequences (outcomes). The original economic evaluation alongside the ROCSS trial will be extended to capture the additional data points on resource use and health-related quality of life information. The potential for increased healthcare costs from managing complications associated with incisional hernia complications, including 'revisits to healthcare' which will include hospital admissions/attendances and any interventions/operations will be investigated.

The preliminary results of the ROCSS trial suggests biological mesh reinforcement was clinically effective but unlikely to be considered cost-effective within 2 years of surgery. However, the long-term patterns in health care resource use and patient quality of life is hypothesised to influence the long-term cost-effectiveness of the mesh intervention.

The analysis will adopt the perspective of the health service and so only direct costs to the health service will be included. In order to estimate the cost for each trial arm, unit costs will be applied to each resource item. Information on unit costs will be obtained from key UK national sources, such as the NHS reference costs, and the Unit costs of Health and Social Care. Where necessary, the unit costs will be inflated to a common price year. The analysis will adopt an incremental approach in that data collection will concentrate on resource use and outcome differences between trial arms.

Two main analyses will be carried out to evaluate the relative cost-effectiveness of biological mesh reinforcement compared to standard closure. A cost-effectiveness analysis will be based on the cost per improvement from the HerQLes tool. In addition, a cost-utility analysis will be carried out and presented in terms of the cost per additional quality adjusted life-year (QALY) gained. QALYs are multidimensional in that they incorporate both the participants' survival and quality of life. The EQ-5D-5L will be administered as part of the telephone follow-up to derive the additional QALY in the two trial arms. The EQ-5D-5L data will be converted using the EQ-5D-3L crosswalk algorithm and UK tariff values will be applied to generate QALYs. As per the original analysis, QALYs will be calculated using the under-the-area curve method. Costs and QALYs will be discounted at an annual rate of 3.5% as per NICE guidelines.

As participants entered the original trial at different time points and the data collection for the extended follow-up study will take place at a fixed time point, the cost and QALY information will be censored. The analysis will use methods such as inverse probability weighting to take into account the censored nature of the data for the cost-utility analysis.

The total costs and consequences of the interventions will be compared using an Incremental Cost-effectiveness Ratio (ICER). For the cost-utility analysis, a threshold of £30,000 per additional QALY gained will be used to assess cost-effectiveness. For the cost-effectiveness analysis, there is no benchmark on the decision maker's willingness to pay for an improvement in the HerQles tool.

The results of these economic analyses will be presented using cost-effectiveness acceptability frontiers to reflect decision uncertainty across different thresholds of willingness-to-pay per additional unit of outcome. Deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the findings to plausible variations in key assumptions and analytical methods used. A

scenario analysis will explore one-off quality of life decrements from the retrospective adverse events from managing hernias (e.g. hospital readmission, reoperation). These retrospective adverse events are likely to impact on participant's quality of life but the gap in data collection has meant that this impact may not be captured.

19.13. Team Structure

ROCSS-EX will have a central Trial Management Group to oversee the delivery of the trial. Each site will have a consultant surgeon PI and at least one local collaborator. This collaborator may be a junior doctor, nurse, or physician assistant. The local collaborators will interrogate local systems to collate routinely collected data on patient interactions with secondary care relating to the stoma site. They will also contact each alive participant to arrange and then complete telephone follow-up.

19.14. Project/research timetable

Total study duration: 14 months

- Set-up phase: Autumn/Winter 2020 - this will include revising the trial protocol, preparation of the patient information sheet and letter, designing new CRFs, building the REDCap database.
- Data collection: Winter 2020-Spring 2021.
- Analysis and report/manuscript preparation: Spring-Summer 2021.

19.15. Ethical and regulatory approvals

The original ROCSS trial received Research Ethics Committee (REC) and Health Research Authority (HRA) approval. The extension of the follow-up beyond 2 years by both telephone consultation and routinely collected hospital data at 5-8 years will be incorporated as a substantial amendment to the existing approval.

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Appendix A: Patient Pathway Summary

1. Patients are **identified** either at the out-patient visit, pre-operative assessment, or from advance theatre lists. Recruitment can be carried out by the principal investigator, operating surgeon, research investigator, Colorectal Nurse Specialist or Stoma nurse. At this appointment, the basic points about the trial are discussed with the patient and they are given a **Patient Information Sheet** (PIS) to take with them.

2. **Consent is taken and documented either at clinic or pre-operatively**. At this time, patients are able to discuss the trial in depth with the Research Investigator. Once consented, the patient completes a baseline **Euroqol EQ-5D and VAS** questionnaire. The Research investigator completes the **randomisation form and pre-operative data form**. Randomisation can be performed at any point pre-operatively.

3. On the day of surgery, the patient is taken to the anaesthetic room. The operation will be carried out using mesh, or not as indicated by the randomisation. The **intra-operative data form** is completed by the Surgeon or Research Investigator.

4. A **follow-up appointment** will be undertaken **30 days after surgery**. This is a routine surgical follow up appointment and the **30 Day Clinical Follow-up assessment** will be completed by the principle or research investigator. As a back-up, a telephone questionnaire will be undertaken in the event that the follow-up appointment is delayed beyond that time frame. Patients will complete **Cost Collection, Euroqol EQ-5D and VAS** questionnaires. The principle or research investigator will **book the follow-up CT** either post-operatively or at the first follow-up appointment.

5. Patients will be telephoned between 9-11 months post-randomisation to remind them about the upcoming appointments at 12 months.

6. A third follow-up face-to-face appointment will be undertaken at 1 year post-randomisation. This is a routine surgical follow-up appointment and a **12 month clinical follow-up form** will be completed. As a backup, a telephone questionnaire will be undertaken in the event that the follow-up appointment is delayed beyond that time frame. Patients will complete **Cost Collection, Euroqol EQ-5D and VAS** questionnaires.

7. Patients will have their follow up CT scan between 9-15 months from the date of randomisation. This will be sent electronically to the central office, or via a hard-copy CD to the Birmingham Clinical Trials Unit. Two blinded radiologists will review the scans and complete the **radiology assessment form**.

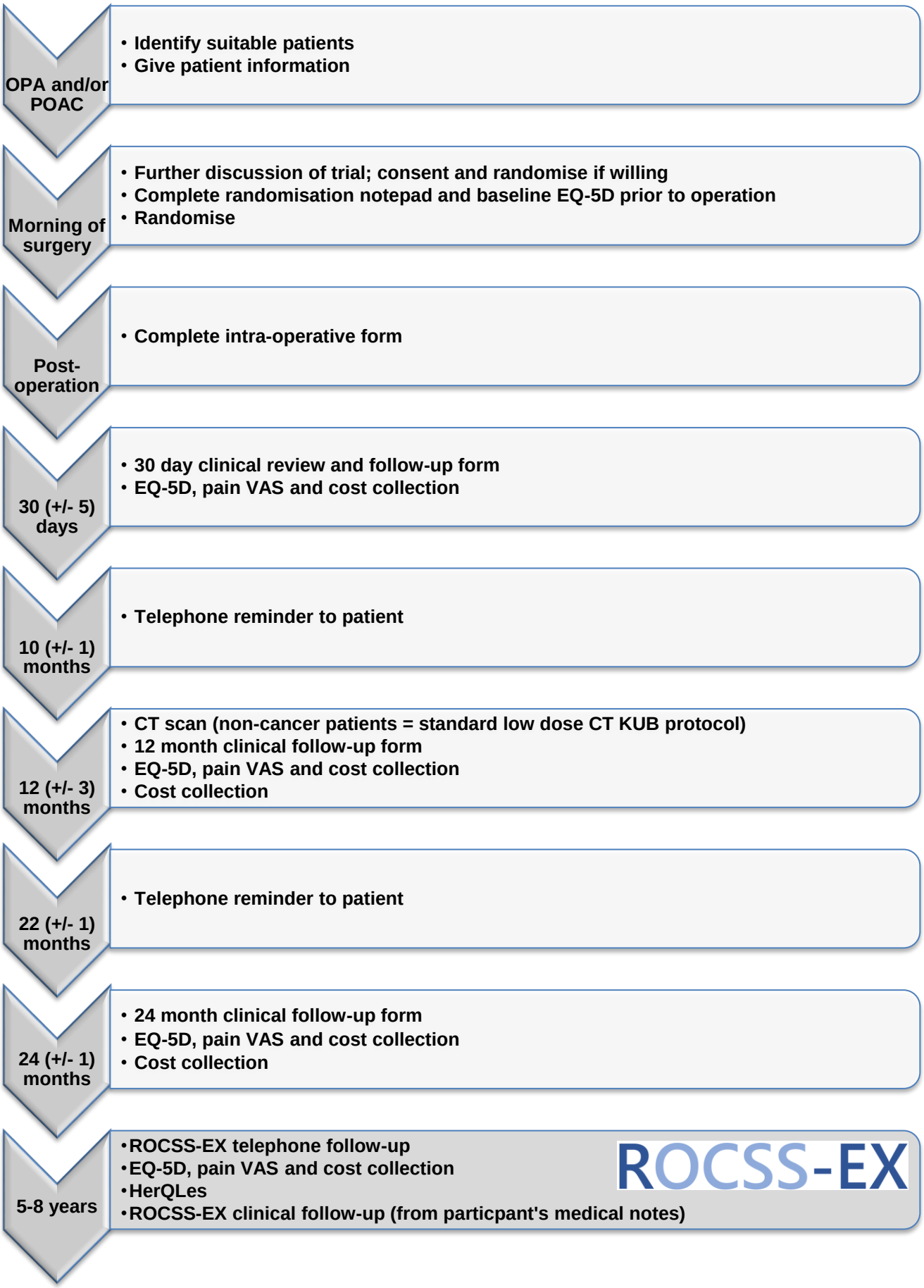
8. Patients will be telephoned between 21-23 months post-randomisation to remind them about the upcoming appointment at 24 months.

9. A fourth and final clinical follow-up will be undertaken at 2 years from randomisation. A **24 month clinical follow-up form** will be completed will be completed. As a backup, a telephone questionnaire will be undertaken in the event that the follow-up appointment is delayed beyond that time frame. Patients will complete **Cost Collection, Euroqol EQ-5D and VAS** questionnaires.

10. **ROCSS-EX**: Extension of follow-up

    Follow-up will be undertaken at 5-8 years from randomisation. A ROCSS-EX clinical follow-up form will be completed using the patient's medical notes. Patient's will be sent the ROCSS-EX Patient Letter and PIS, and then contacted by telephone and the ROCSS-EX telephone follow-up completed. Telephone follow-up will include Euroqol EQ-5D, Pain VAS and HerQles questionnaires.

Patient Pathway Summary



Appendix B: Day of Surgery Pathway

1) Pre-op
    1 Ensure patient consent is completed
    2 Ensure patient is randomised
    3 Ensure mesh available
    4 Ensure randomisation form completed

2) Intra-operatively
    1 Give prophylactic antibiotics (either arm)
    2 Place mesh
        i) Parachute inlay meshes as per recommended surgical technique sheet
        ii) If mesh placed onlay, ensure a drain is left

3) Post-operatively
    1 Complete intra-operative form
    2 Complete one year CT scan request form and book
        i) GI protocol if cancer follow-up (10-14 months acceptable)
        ii) CT KUB follow-up if non-routine scan (12 months)
    3 If a drain was left, remove it when draining <30ml in a 24 hour period
    4 Ensure provision for 30 day follow-up review

Appendix C: Radiology Sub Study Protocol

Sub-study Protocol:

Ultrasound versus Computed Tomography detection of hernia

Background

Hernias can be detected in many ways. These include measures reported by patients, those detected by clinicians, and those detected by imaging methods[1-3]. This has led to uncertainty about which is the best method to use for reporting randomised trials. Since hernias can take many years to become apparent, clinical detection is time-consuming[4]. Surrogate imaging markers may provide earlier delivery of endpoints. This would rely on reliability and reproducibility of imaging modalities, which would need to be clearly correlated with clinical endpoints. Within these controversies, it is unclear if ultrasound (USS) or computed tomography (CT) imaging is the best modality.

One of the secondary endpoints in the ROCSS study is to evaluate the detection rate of stoma site hernias with a CT scan one year after the closure of the stoma. This CT is performed as a 'standard' scan, in a supine position with the patient holding their breath. It is possible that this CT scan will not detect abdominal wall hernia owing to the lack of a 'dynamic' element. In order to address this concern we propose using ultrasound to scan 40 consecutive patients who have undergone their one year follow up CT scan in the Queen Elizabeth Hospital as part of the ROCSS trial. This ultrasound will be performed in a standardised manner corresponding to the standardised clinical examination. We will aim to perform the ultrasound at the same time the patient attends for their CT scan so that they only need to attend the hospital on one occasion. The radiologist will perform the ultrasound examination prior to any review of the CT scan.

Aims

To compare the efficacy of ultrasound versus computed tomography detection of hernia.

Research Questions

What is the correlation between ultrasound detected and computed tomography detected herniation?

1. Does USS or CT detected hernia correlate to a higher degree with clinical detection of hernias?
2. Does USS or CT detected hernia correlate to a higher degree of patient reported hernia?

Design

Recruitment and Consent

Access to participants will be through the Queen Elizabeth Hospital (University Hospital Birmingham NHS Foundation Trust) and through the ROCSS trial with ethical and local R&D approval. Potential participants will be identified by the relevant consultant and researcher.

Sampling

A sample of 40 participants willing to participate in this research will be selected from participants identified as eligible and subsequently consented and randomised into the ROCSS Trial.

Inclusion criteria:

As for the main ROCSS Trial

Exclusion criteria:

As for the main ROCSS Trial

Recruitment:

Participants will be sent an information sheet about the study, and then telephoned to ask if they are willing to participate.

Treatment

A high-resolution linear ultrasound probe will be used to scan the stoma site in the following positions:

- Standing
- Standing with forceful cough
- Standing with Valsalva manoeuvre
- Supine
- Supine with forceful cough
- Supine with Valsalva manoeuvre

Data Collection

The following will be recorded:

1. Is there a hernia present (i.e. a focal protrusion of fat or abdominal content through a defect in the anterior abdominal wall at the site of stoma closure)
2. If a hernia is present we will note:
    a. Whether the hernia contains bowel, fat or other abdominal content.
    b. Size of hernia
    c. Size of the neck of hernia (long axis measured in cm)
    d. Whether any bowel dilatation is seen in association with the hernia
    e. In what position and during what manoeuvre the hernia was identified
3. If no hernia is present we will assess if there is a generalised bulge at the stoma closure site (i.e. the abdominal wall muscles remain intact)
4. Whether a mesh can be identified

Ethical issues

Risks, burdens and benefits

There are no known side-effects of ultrasound, and as such it is considered to be extremely safe. It is used to assess pregnant women and their foetuses at all stages of development without harm.

Data protection and storage

As for the main ROCSS trial

Ethics approval

Ethics approval will be sought from MREC via NRES.

Funding and timescale

This study will be embedded within the main trial, and performed to the same time frame.

References

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4 Burger JW, Luijendijk RW, Hop WC, Halm JA, Verdaasdonk EG, Jeekel J. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. Ann Surg 2004;240(4):578-83; discussion 83-5.

Appendix D: ROCSS Re-consent Decision Tree