**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 v4.0*

8th October 2014
Protocol Summary

Closure of complex and contaminated abdominal wounds is challenging and carries risks, including wound dehiscence and incisional hernias. Use of biological meshes in these situations may provide a safe method of reducing these complications, especially long-term incisional hernias. ROCSS will use stoma site closure as a model for biological mesh placement during any difficult contaminated abdominal wall closures.

Hernia at the site of stoma closure occurs in up to 30% of patients and is associated with adverse effects on quality of life. In up to 10% of cases, patients are submitted to complex re-operation which carries significant morbidity. Not all patients will report symptoms or undergo repair, as they do not wish to have a further major operation. Incisional hernias at the site of stomas closure form an important and well defined subgroup. If there is a measurable benefit from mesh insertion, elective use of a collagen mesh would warrant consideration in the closure of other difficult, 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 be used in future abdominal wall studies as a surrogate endpoint for clinical hernia.

Aim

To assess whether a biological mesh (collagen tissue matrix) reduces the incidence of clinically detectable stoma closure site hernias at two years compared to standard closure techniques.

Primary Outcome

1. Occurrence of clinically detectable hernias at two years post randomisation.

Secondary Outcomes

1. Radiological hernia rate at one year post-randomisation. An exploratory analysis will 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. Surgical re-intervention rate.

3. Surgical complications at 30 days post-operation and 1 year post-randomisation.

4. Quality of life and post-operative pain.

5. Cost-benefit analysis.

Design

560 patients will be randomised over 2 years from at least 30 centres. ROCSS will be a single blind randomised controlled trial with a CT scan at one year and clinical follow up at 2 years. Cost benefit analysis and quality of life analysis will be performed at 2 years.

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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1. Background

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. 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. 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. 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.

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.

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. Complications following reversal include obstruction, wound infection, wound dehiscence, anastomotic leak and the development of incisional hernias. Hernias are a well-recognised complication with known morbidity. 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.

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%) than the secondary endpoint papers (hernia rate 8%). 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. 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.

**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.

**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.

**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\(^\circledR\) is a well-established biological mesh/ tissue matrix which would be compared against a control arm of no mesh placement.

ROCSS will randomise 560 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. Trial 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 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 incisional hernias. 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 and seroma formation, at 30 days post-operatively and 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 in the UK 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 560 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.

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 (Appendix B) and they will be given the opportunity to ask questions.

Once patient eligibility is confirmed, the patient may be consented for 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 (Appendix C) 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 (Randomisation Notepad (Appendix D), EuroQoL EQ-5D (Appendix L), and the pain VAS (Appendix M). After this the patient can then be randomised into the trial (see below). This may be in the outpatient clinic or following admission for surgery.

After consent and randomisation, the patient’s GP will be informed by letter of their patient’s inclusion in the study (Appendix E). 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 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 who will 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 (Appendix D) 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.
7.3 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 F 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 Study 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 Study 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.

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<th>Prior to patient entry/Day of admission for surgery</th>
<th>At surgery</th>
<th>30 days post-op +/-5 days</th>
<th>12 months +/- 3 m</th>
<th>24 months +/- 1 m</th>
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<td>Informed consent</td>
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<td>Clinical examination</td>
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<td>Pre-operative assessment data</td>
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<td>Operative details</td>
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<tr>
<td>Clinical follow-up</td>
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<td>Complications</td>
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<td>Re-interventions</td>
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<td>Resource usage</td>
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<td>Quality of Life &amp; Pain Measures</td>
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<td>CT scan</td>
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At the time of patient entry into the trial, the following data will be collected:

- Demographics (age, gender, BMI, primary indication for stoma, malignancy present or absent)
- Type of stoma to be closed (ileostomy, colostomy)
- First stoma closed on abdominal wall or re-site closed
- 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 (Appendix G) at time of surgery. Post-operative complications will be recorded on the 30-day Post-Operative Follow-up form (Appendix H). The patients will be contacted by telephone by the research team at site prior to the 12 months review to remind them about their upcoming CT scan and review at 12 months.

At 12 and 24 months post-randomisation, Follow-up forms (Appendix I) will be used to collect information on the presence of clinical hernia and re-intervention rates.

A radiological assessment of the presence of hernia will be completed at 12-months post-randomisation (Appendix J). Quality of Life and pain forms (Appendix L and Appendix M) 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 assessments will be performed by a surgeon (qualified to MRCS level or above) who is 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 +/- 2 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 and this scan will also be used to assess for hernia recurrence. In these cases, the cancer follow-up CT can be performed one-year post-randomisation. 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.

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 (i.e. the local radiologist will be unblinded to ensure blinding of the rest of the local clinical team).

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 radiographers.

10.4 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.

10.5 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.

10.6 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.

10.7 End of Trial

The end of the trial for regulatory purposes is defined as the date of the last 2 year clinical follow-up appointment of the last patient undergoing protocol based treatment.
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

11.2 Screening Logs

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

As the feasibility trial is assessing recruitment and randomisation, logs should be kept of all patients who were potentially eligible for entry into the trial i.e. those patients undergoing stoma reversal in that time period, but who were subsequently not randomised. This will provide a denominator when compared to the actual number of patients randomised.

For the full trial, screening logs should also be kept of those patients who were eligible, but who were subsequently missed or refused randomisation and the reasons for doing so.

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 (Appendix K) 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 finishes the study treatment and, when appropriate, until the end of the planned period of follow-up.

12.3 Responsibilities for Reporting of SAEs

The BCTU will report all SAEs to the DMEC at approximately 6-month intervals and to the main REC annually. Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations. Local Investigators do not need to inform the main REC as this will be done by the BCTU.

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\textsuperscript{24}. 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%\textsuperscript{12,13,15}, so this reduction sits at the cautious end of the range.

### 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 will 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 subgroup 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 economic analysis

The health economic analysis will have three distinct parts. The first part is a cost analysis performed as part of the feasibility study; the second is a cost-effectiveness analysis conducted alongside the randomised clinical trial; and the third is a model-based cost-effectiveness analysis, building on the trial-based analysis and using published data on long-term outcomes and costs. A separate health economic analysis will be performed in the UK and other participating countries separately.

15.1 Methods

i) Cost analysis in feasibility study - This analysis will help identify cost drivers for the two strategies to be compared (i.e. collagen tissue matrix versus usual closure techniques). Data on resource use associated with each strategy will be collected and will include information on supplies (e.g. collagen mesh, drains), 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 (e.g. of supplies, inpatient stays, drugs, equipment, equipment and staff) will be collected from published sources such as the National Health Service (NHS) Schedule for Reference Costs, Unit Costs of Health and Social Care (PSSRU), British national Formulary (BNF) and local estimates where possible.

ii) Trial-based analysis - This 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 outcomes will be expressed in terms of cost per hernia clinically detected and cost per additional quality adjusted life (QALY) year gained, both at 2 years. Cost and outcome data will be collected on every patient within the trial.

The cost of stoma site closure will be determined using resource use data collected for each strategy and already identified in (i) above. Any resource items not deemed to be significant cost drivers during the feasibility stage of the study will not be considered in the base case. Resource use information will be collected as part of the trial using a questionnaire and unit cost data will be derived from published and local sources as already indicated in (i). 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-operatively and at 12 and 24 months post-randomisation in order that QALYs can be calculated using the UK tariff (Dolan, 1997).
iii) Model-based analysis - Building on the results of the trial, the model-based analysis will estimate the long-term cost-effectiveness of using collagen tissue matrix for patients undergoing elective closures of stomas. A 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 type and 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. Experts within the team will advise on the final structure of the model.

Costs in the model will include those for the strategies (collagen tissue matrix pathway and usual closure techniques derived from the trial-based analysis), re-admissions (and 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 patient lifetime, with costs and benefits discounted at a rate of 3.5%. The analysis will be conducted from an NHS and personal social services 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 that 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. The Trial Management Group will apply for adoption 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. A funding application for the phase III trial has been submitted to the NIHR Research for Patient Benefit programme (awaiting decision).

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, containing all documentation required to define the involvement of the centre in the trial.
- An Investigators’ folder containing printed 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 reorder 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 1998. 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 15 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. References


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 a Euroqol EQ-5D and VAS questionnaire. 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 a Euroqol EQ-5D and VAS questionnaire.

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. 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 a Euroqol EQ-5D and VAS questionnaire.
**Patient Pathway Summary**

**OPA and/or POAC**
- Identify suitable patients
- Give patient information

**Morning of surgery**
- Further discussion of trial; consent and randomise if willing
- Complete randomisation notepad and baseline EQ-5D and VAS prior to operation
- Randomise

**Post-operation**
- Complete intra-operative form

**30 (±5) days**
- 30 day clinical review and follow-up form
- EQ-5D and pain VAS

**10 (+/- 1) months**
- Telephone reminder to patient

**12 (±3) months**
- CT scan
- 12 month clinical follow-up form
- EQ-5D and pain VAS

**24 (±1) months**
- 24 month clinical follow-up form
- EQ-5D and pain VAS
Summary of an Invitation to take part in a research study called ROCSS.

- Your surgeon is planning on performing an operation to close your current stoma.

- A possible complication after this operation is that a weakness can develop in the abdominal wall where the repair has been made. This occurs in one third of patients and is called a hernia. This can often be repaired by a further operation.

- This hospital is taking part in a national study called ROCSS, which aims to find out whether using a Biologic Mesh, made from natural substances, at the time of your operation, can reduce the risk of a hernia developing in the future.

- One group of patients in ROCSS will undergo standard stoma closure with stitches. The other group will have the mesh inserted to try to reinforce the part of the abdominal wall where the stoma was closed.

- Patients are allocated to both groups at random (like tossing a coin) to make sure the two groups are comparable.

- We are inviting you to take part in ROCSS but you do not have to and if you decide not to this will not affect the quality of your care.

- Please take time to think about whether you want to take part in the ROCSS study. More details are provided below and your medical team will be happy to answer any questions.
An invitation to take part in a research study called ROCSS

We would like to invite you to take part in a research study called ROCSS. Before you decide whether or not you wish to take part in ROCSS, you need to understand why the research is being done and what it will involve for you.

- Part 1 below tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives more detailed information about the conduct of the study.

Please take time to read this information carefully and ask us if there is anything which is unclear or on which you would like more information. Take your time to decide whether or not you wish to take part.

Part 1

What is the purpose of the ROCSS study?

ROCSS stands for ‘Reinforcement of closure of stoma site’. Your surgeon is planning on performing an operation to close your current stoma. One of the possible complications after this operation is that a weakness can develop in the abdominal wall where the repair has been made – this is called a hernia. This can often be repaired by a further operation, but we would like to try and prevent it happening in the first instance.

This hospital is taking part in a national study called ROCSS, which aims to find out whether using a piece of Biologic Mesh (made from natural, absorbable substances) at the time of your operation can reduce the risk of a hernia developing in the future.

What is a hernia? Who gets it?

A hernia is an opening or weakness in the muscular structure of the wall of the abdomen. A hernia causes a bulging of the abdominal wall. This bulging is usually more noticeable when the surrounding muscles are tightened, increasing the pressure in the abdomen. A hernia can occur due to natural muscle weakness or after surgery. Some people develop them
around their stoma. It is thought that up to 30% of people who have a stoma reversed will develop a weakness which may lead to a hernia at the site of the stoma reversal at some point in the future.

**What would be the effects of developing a hernia?**

Some people can have a hernia and never notice it is there. Others may notice a bulge, but not feel they have any other symptoms from it. Some may have pain or tenderness in that area. Hernias can grow larger over time. In a few cases the bowel can get stuck in the hernia, and those patients will require an emergency operation to free the bowel as its blood supply is compromised. In the extreme situations when the bowel loses its blood supply like this, it can make you very unwell and you will need an emergency operation.

**What is a Biological Mesh?**

The Biological mesh we are using in this study comes from pigs’ skin, although all of the cells are removed leaving only the underlying natural structural fibres behind. Once placed inside you by the surgeon, your body will then insert its own cells onto this structure, which is subsequently absorbed away to leave a strong support formed from just your own cells and fibres. Therefore the mesh does not need to be removed once it has been put into place.

**How will it help with the risk of developing a hernia?**

Mesh has been used for a long time to repair many different sorts of hernias. It works by helping the body create new tissue around where the mesh lies, this then helps to support the abdominal wall and hopefully prevent development of a hernia. Biological meshes are a new type of mesh. The advantages of using this sort of mesh is it is absorbed over time, meaning that the mesh will eventually disappear, but it will leave the new tissue which stops the wall becoming weak again. This means that the risk of mesh infection is also reduced.

**What are the alternatives to using Biological Mesh?**

The existing way to close your stoma is to use stitches, although without the support of a mesh, the risk is that a hernia will form. A plastic mesh (as used more commonly for groin hernias) isn’t safe in this situation, as it is at high risk of becoming infected as it can’t be absorbed by your body. The advantage of the Biological Mesh is that your body grows its own cells onto the mesh and eventually absorbs it, so the risk of infection is much lower but the benefits of preventing a hernia remain.
What are the possible risks of using the mesh?

In over 95% of cases there are no problems with using a mesh. In a small number of cases, there is a small risk of infection, this risk is similar to the risk of infection to any wound. There is a small risk that the mesh may become loose or painful, although based on experience of using other meshes this is uncommon. If it does happen, in most cases it will settle down with time, although in some rare cases a further operation may be needed.

What is the purpose of the ROCSS study?

ROCSS stands for ‘Reinforcement of closure of stoma site’. In order to find out if, on balance, the use of the biological mesh at the time of closing a stoma is better than the standard closure methods, we are comparing patients who have had the mesh inserted during surgery with those who have not. We will be assessing the ability of the mesh to reduce the risk of developing a hernia in the future.

Why am I being invited to take part in ROCSS?

Your surgeon will have invited you to take part in ROCSS as you will be undergoing an operation on your bowel to close your stoma. Your surgeon has invited you to take part in the study as they believe the study asks an important question. The ROCSS study is trying to find out if the mesh works or not at reducing the development of hernias. The ROCSS study aims to include at least 560 people like you from hospitals throughout the UK.

Do I have to take part?

No. Taking part in research is voluntary. If you decide to take part you will be given this information sheet to keep and later asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason. If you decide not to take part, then you don’t have to give any reason. Your care will not be affected in any way and you will receive the standard care you would otherwise be given at this hospital. Your surgeons will be happy to talk through any questions you may have regarding ROCSS.

What will happen if I agree to take part in ROCSS?

Most of the treatment you receive will be the same as you would have received even if you were not in a study. There are no extra blood tests or operations required beyond your normal care and there are no additional clinic visits. If you agree to take part in ROCSS we
will go through the study information with you, giving you the chance to ask any questions. You will need to sign a Consent Form if you agree to take part. Your details will then be passed to the ROCSS Study Office at the University of Birmingham. You will also be asked to complete a short questionnaire about your quality of life before your operation, as well as a further questionnaire at 30 days after your operation and 12 and 24 months after entry into the trial.

You will then have your operation and will either have a mesh inserted at the time of surgery or have standard stoma closure. You will not be told which group you are in so as not to influence the results in any way. After your operation you will receive the normal postoperative care, regardless of which group you are in.

Once you have had your surgery we will need to collect information about the operation and any complications (e.g. how long the operation took, if there was any excess bleeding after the operation, if you had any unexpected pain). You will be followed up in clinic and examined by a doctor to assess whether a hernia has developed. Most of this information will be collected at routine out-patient appointments. You will receive one follow up telephone call around 9-11 months after the operation date to remind you about the upcoming CT scan and follow-up appointment. All information collected will be strictly confidential in the same way as your other medical records.

As part of the study, we will ask you to undergo a CT scan at 12 months after entry to the trial. This CT scan is to assess if a hernia has developed which may not have been picked up by a routine clinical examination. This CT scan will be routine for some patients taking part in the study but may be additional for others. The scan involves radiation. The dose from a single CT scan is equivalent to about 3 years of natural background radiation. Any radiation is associated with an increased risk of developing cancer. However the risk associated with a single CT scan is very small (about 1 in 3000) and negligible when compared with the 1 in 4 lifetime risk of cancer.

If you consent, the research staff involved in ROCSS may, in the future, access electronic data from your central NHS records, for example through the Health and Social Care Information Centre (HSCIC). This will provide researchers with information that is routinely gathered and stored during your visits to primary care and hospital, and will allow researchers to find out about your health after the trial has ended and the long-term effects of
The ROCSS trial is designed to compare the effectiveness of biological mesh with no mesh in hernia repair. By using routinely collected data, we can analyze the results without needing to contact you further. However, we need your name, gender, date of birth, and NHS number to proceed with the analysis.

**Can I pick which group to go in (i.e. whether or not biological mesh is used)?**

No. In a randomised clinical trial, each person is assigned to a treatment group randomly (like a lottery). You have an equal chance of being allocated to either the biological mesh or control group. Neither you nor your surgeon can choose which treatment you receive. This ensures a fair comparison between the two groups.

**Who will know which group I am in?**

Only the surgeon involved in the operation will be aware of which group you are in. The other doctors involved in your care, ward nurses, and your GP will know that you participated in the trial but not which group you were allocated to. Your hospital notes will not directly mention your group, except for a special code system decoded by the ROCSS Study Office. The secrecy is maintained to prevent any influence on your care.

**Can I ever find out which group I was in?**

Yes – after your involvement in the study is complete (after the 2 year follow up appointment).

**Part 2**

**What if relevant new information becomes available?**

Sometimes we get new information about the treatment being studied. Your surgeon will discuss how this affects your care and your participation in ROCSS. Your research doctor might consider whether you should continue in the study or withdraw. In either case, the reasons will be explained, and your care will be arranged to continue.
continue in the study he may ask you to sign an updated consent form. If the study is stopped for any other reason, your doctor would, again, tell you and arrange your continuing care.

**What will happen if I don’t want to carry on with the study?**
You can decide not to continue with study follow-up at any time but, if you do, we would still like your data to remain on file and be included in the final study analysis unless you request that they should not be.

**What if something goes wrong?**
If you are harmed by taking part in this research project, there are no special compensation arrangements. If the harm is due to someone's negligence, then you may have grounds for a legal action but you may have to pay for this. Whether or not you take part in the study, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you should ask to speak to the researchers involved in the study who will do their best to answer your questions (contact details are at the bottom of this form). If you remain unhappy and wish to complain formally, you can do this through the normal National Health Service complaints mechanisms, this is usually the Patient Advisory and Liaison Service (PALS). Taking part in the study would not affect your legal rights.

**Will my taking part be kept confidential?**
If you decide to take part in **ROCSS**, all information collected about you during the course of the study will be kept strictly confidential in the same way as all of your other medical records. Information about your operation and follow-up will be sent by your doctors to the **ROCSS** study office at the University of Birmingham Clinical Trials Unit (BCTU), on paper and electronically, where it will be securely stored under the provisions of the 1998 Data Protection Act. This will include a signed copy of your consent form, including your full name. Your GP and the other doctors involved in your clinical care will be notified of your participation in the **ROCSS** trial and kept informed of your progress. We may use national records to track your progress, but otherwise all information about you and your treatment will remain confidential. As we may also contact you by post or telephone to ask you to complete questionnaires asking about your progress, we will ask you to give us your permission to do so. With your permission, your relevant medical notes may be inspected by authorised individuals from the BCTU. They may also be looked at by the sponsor or regulatory authorities. The purpose of this is to check that the study is being carried out correctly.
What will happen to the results of the study?
Once ROCSS has finished we will publish the results in a medical journal so that others can benefit. We will also publicise the results on the study’s website. No individual patients will be identified in any publications. A copy of the published results of the study will be sent to all patients who have participated in ROCSS upon request. In line with clinical trial guidelines, at the end of the study, the data will need to be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made. Should you withdraw consent for your data to be used, it will then be confidentially destroyed.

Who is organising and funding the research?
The ROCSS study was developed by the West Midlands Research Collaborative. The study is coordinated by the ROCSS study office at University of Birmingham Clinical Trials Unit and is sponsored by the University of Birmingham. The research has been approved and reviewed by all of these organisations.

Who has reviewed the study?
All research in the NHS is reviewed by an independent group of people called the Research Ethics Committee to ensure your safety, rights, wellbeing and dignity. This study has been reviewed by the Coventry and Warwickshire Research Ethics Committee.

Where can I get further information?
If you have any further questions about your operation or this clinical trial, please discuss them with your surgeon or the local trial investigator.

Details of local trial investigator/ person to contact:
Name........................................................................................................

Job title.......................................................................................................

Contact Details........................................................................................

The ROCSS study office is located at the University of Birmingham Clinical Trials Unit (BCTU), Public Health Building, University of Birmingham, Edgbaston, Birmingham, B15 2TT.
Web address: www.birmingham.ac.uk/ROCSS; E-mail: ROCSS@trials.bham.ac.uk
Appendix C: Patient Consent Form

ROCSS: Reinforcement of Closure of Stoma Site

Patient Consent Form
Version 5.0 8th October 2014

1. I confirm that I have read and understood the patient information sheet for the ROCSS study (version 5.0 8th October 2014) and have had the opportunity to ask questions.

2. I understand that my participation in this study is voluntary and that I may withdraw at any time, without giving a reason, and without my medical and legal rights being affected.

3. I understand that information about me and my progress will be supplied in confidence to the study coordinators at the University of Birmingham Clinical Trials Unit (CTU) by my own doctors and by NHS registries for use in the ROCSS study. I understand that information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my health status.

4. I agree to a copy of my consent form being sent to the central organisers of the ROCSS study at the University of Birmingham CTU.

5. I understand that my medical notes may be looked at by responsible individuals from the ROCSS study office at the University of Birmingham CTU, or from the sponsor, regulatory authorities or from the NHS trust, where it is relevant to my participation in this study. I give permission for these individuals to have access to my records.

6. I agree to the information held and maintained by The Health and Social Care Information Centre, together with current and future UK NHS bodies, being used in the future to provide information about my long-term health status and health care. For this purpose, I agree to the University of Birmingham CTU holding my name, gender, date of birth and NHS number.

7. I understand that the study researchers will contact me by telephone or post to remind me to complete the questionnaires and to ask me questions over the telephone and that my will be passed to the University of Birmingham CTU for the sole purpose of issuing the trial questionnaires.

8. I understand that my GP will be informed of my participation in the study and may be contacted to provide information about my progress, in confidence, to the central organisers.

9. I understand that I will be randomised between the biological mesh arm and the traditional treatment arm. I understand that being randomised means that neither I nor my surgeon can pick which of the two treatments I will receive.

10. I understand that I will not be told which group I am in until my participation in the study is finished after 2 years.

11. I understand that I will be asked to return to hospital 12- and 24-months after I enter the study for follow-up assessments and that the 12-month assessment includes a CT scan.

12. I agree to take part in the ROCSS study.

Name of Participant: …………………………………

Signature: ……………………………………… Date:……………………………………

Name of Clinician: …………………………………

Signature: ……………………………………… Date:……………………………………
### Appendix D: Randomisation Notepad & Pre-Operative Information

#### Randomisation Notepad and Pre-Operative Information

| Patient forename: __________________________ | Date randomised: __________________________ |
| Patient surname: __________________________ | Responsible surgeon: ______________________ |
| Date of birth: _____________________________ | Hospital: _________________________________ |
| Hospital no.: _____________________________ | NHS no.: _________________________________ | Sex: □ Male □ Female |

1. Is the patient undergoing an elective stoma closure? [Yes] [No]
2. Is a midline laparotomy being planned? [Yes] [No]
3. What type of stoma is being closed? [Ileostomy] [Colostomy]
4. Is a primary or secondary skin closure planned? [Primary] [Secondary]

#### Patient and Surgery Characteristics

| 5. What was the original indication for stoma? | Cancer [□] Non-cancer [□] |
| 6. What is the type of stoma opening? | Loop [□] End [□] |
| 7. Which side is the stoma being close on? | Right [□] Left [□] |
| 8. Is a parastomal hernia evident? [Yes] [No] |
| 9. Is a midline incisional hernia evident? [Yes] [No] |
| 10. What is the patient’s BMI? (BMI: mass (kg)/ height² (metres)) | BMI: ________ |

#### Eligibility Criteria

**If shaded boxes are ticked, patient is not eligible to be randomised**

11. Does patient have a known adverse reaction to porcine products? [Yes] [No]
12. Is the patient participating in any other clinical studies related to the surgical procedure? [Yes] [No]
13. Does the patient have familial adenomatous polyposis (FAP)? [Yes] [No]
14. Will a mesh repair definitely be required (e.g. large parastomal hernia)? [Yes] [No]
15. Has the patient given written informed consent? [Yes] [No]
16. Version of the consent form used? __________________________

#### Randomisation

17. Name of the clinician taking written informed consent: __________________________
18. Name of person randomising patient: __________________________
19. Name of operating surgeon: __________________________
20. ROCSS Trial number: __________________________

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Thank you for completing this CRF. Please return to: ROCSS Study Office, Birmingham Clinical Trials Unit (BCTU), University of Birmingham, Edgbaston, Birmingham, B15 2TT

**ROCSS Trial – Randomisation Notepad**

**CONFIDENTIAL WHEN COMPLETED**

**Version 2.0, 15th April 2014**

---

38
Dear Dr ..............................................
Name.................................................................................. D.O.B....../....../......
NHS No................................................

Your patient, named above, has given their consent and subsequently been enrolled in the ROCSS trial whilst undergoing treatment at this surgical unit.

The ROCSS trial (Reinforcement of Closure of Stoma Site) is a prospective, multicentre, double-blind randomised control trial which aims to find out whether the prophylactic use of biological mesh at the time of stoma closure can reduce the rate of subsequent hernia formation.

Secondary issues to be explored include infection rate, length of hospital stay and need for reoperation. All adult patients undergoing elective stoma reversal (both open and laparoscopic) under the care of a trial participating surgeon are being approached to enter the study. Patients who agree to take part (after full counselling and provision of a patient information leaflet) are then randomised immediately prior to their operation in a 1:1 ratio to the intervention (biological mesh used) or control (traditional technique) arm. Follow-up is according to a predetermined schedule, using specific proformas to collect the blinded data. Your patient will have clinical follow-up at 12 and 24 months with a CT scan at 10-14 months.

ROCSS was developed by the West Midlands Research Collaborative and the University of Birmingham Clinical Trials Unit. The University of Birmingham Clinical Trials Unit are acting as coordinating centre. The study is funded by an educational grant from LifeCell Incorporated. The trial has been approved by Coventry and Warwickshire Research Ethics Committee.

Due to the blinded nature of the study we are unable to inform you which arm your patient has been randomised to (and thus whether biological mesh was used). This information will be made available, if desired, once your patient’s involvement is complete (around 2 years post-operation).

If you require any further information about the ROCSS trial, please either contact me or the ROCSS study office at the University of Birmingham Clinical Trials Unit. Please file this letter in the patient’s notes. I would appreciate being notified if they are no longer one of your patients.

Many thanks,

Name…………………………………………………………………………………………
Position…………………………………………………………………………………………
Contact Details…………………………………………………………………………………………

ROCSS Study Office, Birmingham Clinical Trials Unit, University of Birmingham, Edgbaston, B15 2TT Tel: 0121 415 9105 E-mail: roc@contacts.bham.ac.uk

Appendix E: GP Letter
Appendix F: Day of Surgery Pathway

1) Pre-op
   a) Ensure patient consent is completed
   b) Ensure patient is randomised
   c) Ensure mesh available
   d) Ensure randomisation form completed

2) Intra-operatively
   a) Give prophylactic antibiotics (either arm)
   b) 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
   a) Complete intra-operative form
   b) 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)
   c) If a drain was left, remove it when draining <30ml in a 24 hour period
   d) Ensure provision for 30 day follow-up review
Appendix G: Intraoperative Form

Intraoperative Form

Please complete this form immediately after the patient has surgery

ONLY TO BE COMPLETED BY THE OPERATING SURGEON

Patient initials: ___________________ Patient trial number: ___________________ Date of birth: ___ / ____ / ______

Hospital No.: ___________________ Hospital: ___________________  

Responsible surgeon: ___________________

Surgery
1. Date of surgery: ___ / ____ / ______ (dd / mmm / yyyy) 
2. What was the duration of surgery (to the nearest 10mins)? ________________ mins
3. Skin closure: Skin fully closed ☐ Skin left open (partially/completely) ☐
4. Was a midline incision performed? Yes ☐ No ☐
5. Was there evidence of a parastomal hernia? Yes ☐ No ☐
6. What was the maximum size of the fascial defect? <4cm ☐ 4 - 7cm ☐ >7cm ☐
7. Was there evidence of a midline hernia? No ☐ Yes, suture repair ☐ Yes, repaired with a separate mesh ☐
8. Was the stoma successfully reversed and the site closed? Yes ☐ No ☐
   If not, why not? ____________________________________________________________

Use of Strattice Mesh™
9. If the patient was randomised to mesh, was a mesh used? Yes ☐ No ☐
    If not, why not? ____________________________________________________________
10. If the patient was in the control arm, was a mesh placed anyway? Yes ☐ No ☐
    If yes, why? ________________________________________________________________
11. Was this sublay (inside the peritoneal cavity)? Yes ☐ No ☐
    If no, was it: (i) between the peritoneum and posterior rectus sheath? Yes ☐ No ☐
        (ii) above the posterior rectus sheath? Yes ☐ No ☐
        (iii) above the anterior rectus sheath? Yes ☐ No ☐

12. Size of mesh placed: 10 x 6 cm ☐ or 15 x 10 cm ☐

Complications
13. Were there any other complications related to surgery or the use of mesh? Yes ☐ No ☐
   If yes, please specify? _______________________________________________________

Form completed by: ___________________ Date form completed: ___ / ____ / ______ (dd / mmm / yyyy)

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Date: ___________________ Initials: ___________________ Date: ___________________ Initials: ___________________
# Appendix H: 30 day clinical follow up form

## 30 day Clinical Follow up Form (by blinded assessor)

**Patient initials:** __________  **Patient trial number:** __________  **Responsible surgeon:** ________________

**Date of birth:**  __/___/____  **Hospital:** ___________________

---

**Please complete this form at 30 day follow-up**  **Date of follow-up:** __/___/____

### Part A

1. Did the patient experience any complications that required or prolonged hospitalisation, were fatal or life threatening?  
   - Yes ☐  
   - No ☐
   (If yes, please complete an SAE Form)

2. Death within 30 days?  
   - Yes ☐  
   - No ☐
   (If yes, please complete an SAE Form)

3. Was any further surgery or other procedure related to the closed stoma site required?  
   - Yes ☐  
   - No ☐
   (e.g. drainage of seroma)

4. Has the patient undergone any other subsequent surgery?  
   - Yes ☐  
   - No ☐
   If yes, please specify: ____________________________________________________________

5. Has the stoma site wound epithelialised?  
   - Yes ☐  
   - No ☐

6. Has there been a wound infection of stoma site, defined as any ONE of:  
   - Yes ☐  
   - No ☐
   (i) At least two of: pain or tenderness; localised swelling; redness; heat; fever; AND  
   (ii) The incision is opened deliberately to manage infection or the clinician diagnoses a surgical site infection  
   (c) wound organisms AND pus cells from aspirate/swab

7. Has there been evidence of an anastomotic leak after reversal?  
   - Yes ☐  
   - No ☐
   (i) If yes, was this?  
     - Clinical ☐  
     - Operative ☐  
     - Radiological ☐
   (ii) If yes, how was it managed?  
     - Operatively ☐  
     - Non-operatively ☐

8. Other complications?  
   - Yes ☐  
   - No ☐
   If yes, date:  __/___/____
   If yes, please specify: ____________________________________________________________

### Part B

9. EQ-5D and pain VAS questionnaire completed?  
   - Due at 30 days post-op  
   - Yes ☐  
   - No ☐
   If not, why not? ____________________________________________________________

10. Who performed the 30 day review? ___________________________________________

---

**Form completed by:** ______________________  **Date form completed:** __/___/____

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## Appendix I: Follow Up Form (12 and 24 months)

### Follow-Up Form (by blinded assessor)

To be completed at 12 and 24 months

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Is this the 12 or 24 month follow-up visit? □ 12mth □ 24mth Date of follow-up: __/___/____ dd mmm yyyy

### Part A – ALL PATIENTS

1. (i) Has the patient died? Yes □ No □
   (ii) If yes, date of death: __/___/____ dd mmm yyyy
   If no, date last seen: __/___/____ dd mmm yyyy

2. Has the stoma site wound healed completely? Yes □ No □

3. Is there a hernia at the closed stoma site? (Please refer to ROCSS protocol, p16)
   (i) A palpable fascial defect with or without protrusion of bowel or fat Yes □ No □
   (ii) A global weakness around the stoma scar, without palpable fascial defect. Yes □ No □

4. Does the patient describe any ongoing:
   (i) bulging or similar symptoms at the closed stoma site (e.g. on straining or coughing) Yes □ No □
   (ii) Discomfort at the closed stoma site Yes □ No □

5. Has there been any evidence of seroma formation at any stage? Yes □ No □
   If yes, was diagnosis: Clinical? Yes □ No □ Radiological? Yes □ No □
   Was intervention required? Yes □ No □
   If yes, type of intervention?
   - Aspiration Yes □ No □
   - Surgical drainage Yes □ No □
   - Antibiotics Yes □ No □

6. Did the patient experience a wound infection at the stoma site? Yes □ No □
   If yes, approximated date of diagnosis: __/___/____ (dd mmm yyyy)

7. Has the patient undergone a subsequent operation to repair a hernia at the stoma site? Yes □ No □
   If yes, date of surgery: __/___/____ dd mmm yyyy

8. Has the patient undergone any other subsequent surgery or procedures related to the closed stoma site? Yes □ No □
   If yes, please specify: __________________________ Date: __/___/____ dd mmm yyyy

9. Has the patient had any other subsequent unplanned hospital admissions? Yes □ No □
   If yes, please specify: Abdominal pain □ Bowel obstruction □ Wound infection □ Mesh protrusion □

### Part B – ALL PATIENTS

9. EQ-5D and pain VAS questionnaire complete? Due at 12 and 24 months post randomisation Yes □ No □
   If not, why not? __________________________________________________________

Form completed by: __________________________ Date form completed: __/___/20___

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Appendix J: Radiological Follow Up Form

Radiological Follow-up
To be completed centrally by a blinded Radiologist

Patient initials: __________________ Hospital Number: __________________ ROCSS Trial Number: ____________

Part A
1. Date of operation: ____________/mm/______
   dd mmm yyyy
2. Date of CT scan: ____________/mm/______
   dd mmm yyyy
3. Was IV contrast used? Yes ☐ No ☐
4. Slice thickness reviewed (mm): ________mm (maximum 5mm)

Part B
5. Stoma repair site evident? Yes ☐ No ☐ Inadequate view ☐
6. Depth of tissue between skin and most superficial muscle layer at stoma site _______ cm is there herniation of intra-abdominal contents (fat or other) into abdominal wall subcutaneous fat?
   Yes ☐ No ☐ Inadequate view ☐
   If yes: 7a) Hernia location: Right iliac fossa? Yes ☐ No ☐
           Left iliac fossa? Yes ☐ No ☐
           Midline? Yes ☐ No ☐
   7b) Hernia content: Fat ☐ Bowel ☐ Other ☐
   If other, please specify ____________________________
   7c) Size: Cranio-caudal diameter (cm): _______ cm (between 1 and 10cm)
        Transverse diameter (cm): _______ cm by _______ cm (between 1 and 10cm)
        Hernia neck size (cm): _______ cm (between 1 and 10cm)
8. Is there a bulge at the stoma site present? Yes ☐ No ☐ Inadequate view ☐
   If yes: 8a) Bulge location: Right iliac fossa? Yes ☐ No ☐
           Left iliac fossa? Yes ☐ No ☐
           Midline? Yes ☐ No ☐
   6b) Bulge content: Fat ☐ Bowel ☐ Other ☐
   If other, please specify ____________________________
   6c) Size: Cranio-caudal diameter (cm): _______ cm (between 1 and 10cm)
        Transverse diameter (cm): _______ cm by _______ cm (between 1 and 10cm)
9. Is mesh evident radiologically? Yes ☐ No ☐
10. Other significant findings (e.g. bowel adherent to stoma site) ______________________________________

Form Completed by: _____________________________ Date form completed: _____/_____/_______

FOR TRIALS OFFICE USE ONLY:

Received: ___________________ Entered: ___________________
Date Initials Date Initials

Checked: ___________________
Date Initials

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ROCSS Radiology Follow-Up Form

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Appendix K: Serious Adverse Events Form

Serious Adverse Events Form

Please report within 24 hours any SERIOUS ADVERSE EVENTS by completing the details below and faxing this form to the ROCSS trial office on fax: 0121 415 8871. Once you have faxed the form, please send (with copies of relevant reports) to the ROCSS Trial Office, University of Birmingham Clinical Trials Unit, College of Medical and Dental Sciences, Public Health Building, University of Birmingham, Edgbaston, Birmingham, B15 2TT

Patient initials: ___________ Patient trial number: _______ Responsible surgeon: _______________________

Date of birth: ___________ Hospital: ________________________________________________________________

Part A: SAE Description

1. Is this an initial, follow-up or final report?
   Initial report ☐ Follow-up report ☐ Final report ☐

Reason for Reporting:

2. Death? Yes ☐ No ☐ Date of death: __/____/____

3. Life-threatening event? Yes ☐ No ☐

4. Inpatient hospitalisation or prolonged existing hospitalisation? Yes ☐ No ☐
   (i) If yes, number of days? _____ days

5. Persistent or significant disability/incapacity? Yes ☐ No ☐

6. Other pertinent medical reason for reporting? Yes ☐ No ☐
   (i) If other, please specify:
       ________________________________________________________________________________________
       ________________________________________________________________________________________

7. Date event started: __/____/____  Date event ceased: __/____/____

8. Details of adverse event, please attach copies of relevant reports:
   ________________________________________________________________________________________
   ________________________________________________________________________________________
   ________________________________________________________________________________________
   ________________________________________________________________________________________
   ________________________________________________________________________________________
   ________________________________________________________________________________________
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   ________________________________________________________________________________________
Part B: Trial Treatment
To be completed by responsible Doctor

9. If SAE considered to be related to the use of mesh, please assess causality:
   (i) Not related to use of mesh
   (ii) Unlikely to be related to use of mesh
   (iii) Probably related to use of mesh
   (iv) Definitely related to use of mesh

10. Please give reasons if you consider event to be related to use of mesh:

Part C

Signature of person reporting: ________________________________
Date: __/____/____

You must have signed the site delegation log

Name: ____________________________
Position: _________________________
Telephone number: __________________

Signature of Investigator: ____________________________
Date: __/____/____
If not completed by Investigator

Part D:
TRIAL OFFICE USE ONLY

1. SAE reference number: ______________________

2. Date reported to the trial office: __/____/____
   dd mmm yyyy

3. Date reported to CI: __/____/____
   dd mmm yyyy

4. Date reply received from CI: __/____/____
   dd mmm yyyy

5. Is this an SAE? Yes ☐ No ☐

6. CI comments:
   ____________________________________________
   ____________________________________________
   ____________________________________________

7. Date due to be reported to REC: __/____/____
   dd mmm yyyy

Thank you for completing this CRF. Please return to: FREEPOST RRKR-JUZR-HZHG ROCSS Study Office, Birmingham Clinical Trials Unit, University of Birmingham, Edgbaston, Birmingham, B15 2TT

ROCSS Trial – SAE Form
Version 2.2 08th October 2014
Appendix L: EuroQoL EQ-5D

Health Questionnaire

(English version for the UK)

(Validated for use in Eire)

Patient initials: __________
Date of birth: ___/___/___
Hospital: __________
Responsible clinician: __________
Hospital number: __________
NHS number: __________
ROCSS number: __________

Gender: □ Male □ Female

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By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** *(e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
Appendix M: Pain Visual Analogue Scale

Pain (relating to stoma site) Visual Analogue Scale

To help you describe whether you are in pain or not, we have drawn a scale (rather like a thermometer) on which the worst possible pain you can imagine is marked 100 and no pain at all is marked 0.

We would like you to indicate on this scale how much pain you are in today, relating to the site where your stoma used to be. Please do this by drawing a line from the box below to whichever point on the scale you feel best describes how much pain you are in today.

My pain rating today is:

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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. 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. 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**

1. What is the correlation between ultrasound detected and computed tomography detected herniation?
2. Does USS or CT detected hernia correlate to a higher degree with clinical detection of hernias?
3. 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
We would like to invite you to take part in our research study. Before you decide, it’s important for you to understand why we’re doing this research, and what participation would involve for you. Please take the time to read this information sheet carefully, and feel free to speak to others about the study if you wish. If you would like more information on any aspect of the study, or if there is anything in this information sheet that you don’t understand, then please ask us.

What is the purpose of the research?
Researchers are not sure of the best method for detecting a hernia. It may be when doctors examine you, or it may be through special scans. We plan to compare two type of scan – computed tomography (CT) and ultrasound – to see which is best. You will already be having the CT scan as part of the ROCSS trial.

Why have I been invited?
You have been invited to take part as you are taking part in the ROCSS Trial. This sub-study aims to include 40 participants being treated at the Queen Elizabeth Hospital, Birmingham.

Do I have to take part?
You do not have to participate in this study if you don’t want to. It is entirely up to you whether or not you do so. Once you’ve had time to read this information sheet and to think, we’ll telephone you to ask if you’d like to take part in the study. We’ll ask you to sign a consent form to show that you’ve agreed to take part. If you decide not to take part, then you don’t have to give any reason. Neither your medical care nor on-going participation in the ROCSS trial will be affected by whether or not you help us with our research.

What will happen to me if I take part?
If you agree to take part, we will go through the study information with you, giving you a chance to ask any questions. You will need to sign a consent form if you agree to take part. Your details will be passed to the ROCSS Study office at the University of Birmingham.

You will then undergo one extra scan, an ultrasound scan, at the same time as your CT scan. The ultrasound scan will take around 20 minutes. We will try to schedule it on the same day as your CT scan to save you time.

What are the possible risks and disadvantages of taking part?
There are no disadvantages or risks in taking part in this study and participation will not change your treatment in any way. Ultrasound scans are extremely safe with no known side-effects. It does not hurt, and involves no injections. It is the same type of scan used for pregnant women.

What are the possible benefits of taking part?
We cannot promise this study will help you but with the information that we get from this study we hope to improve the treatment of patients with hernia.

What will happen if I decide not to continue with the study?
You are free to withdraw from the study at any time without giving a reason. Your treatment will not be affected in any way.
What if there is a problem?
If you have concerns about the study or about how you have been treated by the researcher please contact the research team. Details are provided below. If you are still unhappy you can make a formal complaint through the NHS Complaints Procedure. Details can be obtained from your local hospital.

Will my taking part in the study be kept confidential?
Yes. All information collected about you during the course of the study will be kept strictly confidential in the same way as all of your other medical records. Information about your participation in the study will be sent by your doctors to the ROCSS study office at the University of Birmingham Clinical Trials Unit (BCTU), where it will be stored securely in accordance with the 1998 Data Protection Act. With your permission, your relevant medical notes may be inspected by authorised individuals from the BCTU. They may also be looked at by the sponsor or regulatory authorities. The purpose of this is to check that the study is being carried out correctly.

What will happen to the results of the research study?
Once ROCSS has finished we will publish the results in a medical journal so that others can benefit. We will also publicise the results on the study’s website. No individual patients will be identified in any publications. A copy of the published results of the study will be sent to all patients who have participated in ROCSS upon request. In line with clinical trial guidelines, at the end of the study, the data will need to be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made. Should you withdraw consent for your data to be used, it will then be confidentially destroyed.

Who is organising and funding the study?
The ROCSS study was developed by the West Midlands Research Collaborative. The study is coordinated by the ROCSS study office at University of Birmingham Clinical Trials Unit and is sponsored by the University of Birmingham. The research has been approved and reviewed by all of these organisations.

Who has reviewed the study?
All research in the NHS has been looked at by independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by a Research Ethics Committee.

What do I do if I want to participate, find out more or complain?
If you have any further questions about your operation or this clinical trial, please discuss them with your surgeon or the local trial investigator.

Details of local trial investigator/ person to contact:
Dr Colm Forde
Consultant Radiologist
Queen Elizabeth Hospital, Birmingham
Email colm.forde@uhb.nhs.uk
Tel: 0121 371 2366

The ROCSS study office is located at the University of Birmingham Clinical Trials Unit, Public Health Building, University of Birmingham, Edgbaston, Birmingham, B15 2TT.
Web address: www.birmingham.ac.uk/rocss; e-mail: ROCSS@contacts.bham.ac.uk
Sub-study Participant Consent Form:
Ultrasound versus Computed Tomography detection of hernia

1. I confirm that I have read and understand the information sheet dated 8\textsuperscript{th} October 2014 (version 1.0) for the above study and have had the opportunity to consider the information and ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, and without my medical care being affected.

3. I understand that information about me and my progress will be supplied in confidence to the study coordinators at the University of Birmingham Clinical Trials Unit (CTU) by my own doctors for use in the ROCSS study.

4. I agree to a copy of my consent form being sent to the central organisers of the ROCSS study at the University of Birmingham CTU.

5. I understand that relevant sections of my medical notes and the data collected may be looked at by responsible individuals from the University of Birmingham or from the Sponsor or from regulatory authorities or from the NHS Trust, where it is relevant to my participation in this study. I give permission for these individuals to have access to my records.

6. I understand that the study researchers may contact me by telephone about the study and to ask me questions over the telephone.

7. I understand that the information will be used for medical research only and that I will not be identified in any way in the analysis and the reporting of results.

8. I agree to take part in the above study.

Name of participant: ...........................................................................................................................

Signature: ............................................................ Date: ..............................................................

Name of person taking consent: ...........................................................................................................

Signature: ............................................................ Date: ..............................................................
### Appendix O: Radiology Sub Study Follow-up Form

**Radiological Sub-study Follow Up Form**

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2. Date of operation: 

3. Date of ultrasound scan: 

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))

   - Yes ☐
   - No ☐

   If **yes**: Hernia location:
   - Right iliac fossa? Yes ☐
   - Left iliac fossa? Yes ☐
   - Midline? Yes ☐

   Cranio-caudal diameter (cm): ______ cm *(between 1 and 10cm, long axis measured in cm)*

   Transverse diameter (cm): ______ cm by ______ cm *(between 1 and 10cm, long axis measured in cm)*

   Hernia neck size (cm): ______ cm *(between 1 and 10cm, long axis measured in cm)*

2. If hernia present, hernia content:

   - Fat ☐
   - Bowel ☐
   - Other ☐

   If other, please specify: __________________________________________________________

3. Is mesh evident radiologically?

   - Yes ☐
   - No ☐

4. Other significant findings *(e.g. bowel adherent to stoma site)*

   __________________________________________________________

   __________________________________________________________

5. When is hernia detectable? (tick all that apply):

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

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Form Completed by: ___________________________ Date form completed: ___/___/____

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Thank you for completing this CRF. Please return to: FREEPOST RRKR-JUZR-HZHG ROCCS Trial Office, Birmingham Clinical Trials Unit, University of Birmingham, Edgbaston, Birmingham, B15 2TT

ROCSS Trial – Radiology Sub-Study – Follow Up Form 1.0 8th October 2014

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