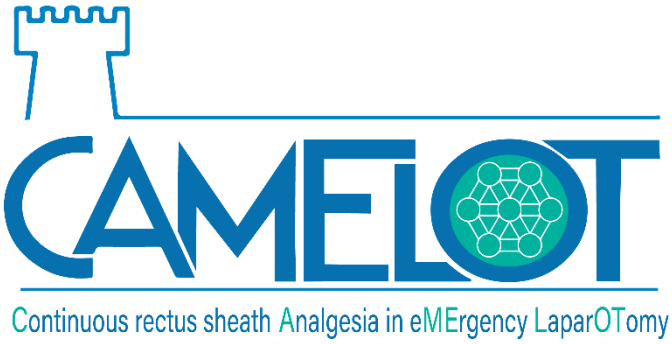

CAMELOT - Continuous rectus sheath Analgesia in eMErgency LaparOTomy

Multi-centre, randomised sham-controlled trial of rectus sheath catheter-delivered local anaesthetic infusion compared with usual care in patients undergoing emergency bowel surgery

Funder	National Institute for Health Research (NIHR133554)
IRAS Number	312553
ISRCTN number	ISRCTN15475290

This protocol has regard for the Health Research Authority guidance

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Glossary/abbreviations

AE	Adverse event
AR	Adverse reaction
ASGBI	Association of Surgeons of Great Britain & Ireland
BPI	Brief pain inventory
BTC	Bristol Trials Centre
CI	Chief Investigator
CRF	Case report form
DMSC	Data monitoring and safety committee
ELLSA	Emergency Laparotomy and Laparoscopic Scottish Audit
EQ5D-5L	EuroQol 5 dimension 5 level questionnaire
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICH-GCP	International conference for harmonisation of good clinical practice
ITT	Intention-to-treat
LPLV	Last patient last visit
MRC	Medical Research Council
NELA	National Emergency Laparotomy Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRS	Numerical rating score
OBAS	Overall Benefit of Analgesic Score
PCA	Patient controlled analgesia
PIL	Patient information leaflet
PI	Principal Investigator
POMCTN	Perioperative Medicine Clinical Trials Network
QALYs	Quality adjusted life years
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event.
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial Master File
TMG	Trial management group
TSC	Trial Steering Committee
UHS	University Hospital Southampton NHS Foundation Trust
UOB	University of Bristol
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1 Trial Summary

Short title	CAMELOT Trial
Design	Multi-centre, pragmatic, randomised controlled trial with blinding of patients and outcome assessors, and patient follow-up for 6 months.
Research sites	Acute surgical services in secondary and tertiary care NHS hospitals.
Objectives	To establish if the use of rectus sheath catheter-delivered local anaesthetic infusion in addition to standard analgesia, is superior to standard analgesia without RSC as defined by the Overall Benefit of Analgesia Score (OBAS) over the first 5 postoperative days.
Sample size	750 randomised participants (375 per group) This sample size will provide 90% power to detect a 15% relative reduction in mean OBAS assuming a standard deviation (on the logarithmic scale) of 0.65; 5% statistical significance and allowing for 10% missing data.
Inclusion criteria	Adults 18 years or over, undergoing emergency laparotomy surgery via a midline incision and eligible for inclusion in the National Emergency Laparotomy Audit (NELA)
Exclusion criteria	Clinician or patient refusal, planned epidural anaesthesia, contraindications to RSC including allergy to local anaesthetic (LA), anatomical factors making RSC insertion impossible.
Intervention	Insertion of RSCs with infusion of LA for 72 hours from the end of surgery
Comparator	Sham RSCs with inactive infusion device in place for 72 hours from the end of surgery
Statistical Analysis	The primary analyses will be by intention to treat and results will be reported in line with the CONSORT guidelines. The economic evaluation will be conducted from an NHS perspective at 6 months post-randomisation.
Trial duration	56 Months

2 Background/Rationale

In the UK, around 30,000 patients each year undergo a major surgical operation called an emergency laparotomy to treat an acute life-threatening problem within the abdomen. During the procedure, a large, vertical midline incision is made into the abdomen to allow the surgeon to diagnose and treat serious conditions including internal bleeding, sepsis or a blockage to the bowel. Whilst the midline incision provides quick and easy access to the abdominal cavity, it cuts the nerves crossing the abdominal wall, causing severe postoperative pain, hindering early recovery and discharge.

Intravenous, opioid-based, patient-controlled analgesia is used to treat post-operative pain following emergency laparotomy. It involves administration of a programmed dose of analgesics, while also allowing patients to receive additional, need-based doses at a particular time when pain is likely to increase. Opioids have many side effects, including nausea, constipation and respiratory depression, which are associated with slower recovery and discharge times.

Rectus sheath blockade is a promising modality for opioid-sparing pain relief following midline incision laparotomy. However, there is limited randomised controlled trial (RCT) data and none in the emergency setting. An NIHR-funded pilot RCT compared RSCs with epidural analgesia in elective major abdominal surgery, recruiting 131 patients (1). The RSC group reported good overall satisfaction with pain management. The intervention was safe, with only one reported serious adverse event (SAE) and the embedded qualitative study found that RSCs were acceptable to patients and highlighted the importance of staff training in the intervention.

The study reported a 1.8-day mean decrease in length of hospital stay in the RSC group, while RSC material costs were modest (2). The data from the pilot suggest a favourable clinical and health economic profile with RSC. Superior analgesia could impact both patient satisfaction and the incidence of postoperative complications and time spent in hospital. Given that the majority of the total ~£10k inpatient cost of emergency laparotomy is due to the duration of critical care and hospital stay (3,4), a modestly-priced intervention such as RSC that may speed postoperative recovery has the potential for major health economic impact.

To inform the protocol for CAMELOT, the trial team conducted a survey of anaesthetists and surgeons involved in the care of emergency laparotomy patients to assess current practice and views on the trial. The survey was distributed to stakeholder organisation members (UK Perioperative Medicine Clinical Trials Network [POMCTN], National Emergency Laparotomy Audit [NELA], and the Association of Surgeons of Great Britain and Ireland [ASGBI]) and 213 responses were received. According to our survey there is currently only partial uptake of RSCs as routine practice across NHS hospitals, with only 22% of respondents stating that they use RSC in >75% of patients undergoing emergency laparotomy surgery. The survey also confirmed good levels of clinical community and individual level equipoise with 80% of respondents willing to take part in a trial evaluating RSC in this patient group.

3 Trial Objectives

3.1 Primary Objective

To assess whether the use of rectus sheath catheter (RSC)-delivered local anaesthetic infusion in addition to standard analgesia, is superior to standard analgesia without RSC for postoperative pain control in adult patients undergoing emergency laparotomy surgery.

3.1.1 Primary outcome measure

The mean Overall Benefit of Analgesia Score (OBAS) over the first 5 postoperative days.

OBAS is a patient-reported composite endpoint of pain scores, opioid side-effects, and patient satisfaction (range 0 [best] to 28 [worst]) (5,6).

3.2 Secondary Objectives

To estimate the difference between groups with respect to a range of patient-reported and clinical secondary outcomes and to estimate the cost-effectiveness of RSC (plus standard analgesia) compared to standard analgesia alone.

3.2.1 Secondary outcome measures

All outcomes are measured from the date of randomisation unless indicated otherwise.

- Postoperative complications with severity of Clavien-Dindo grade II or higher within 30-days (see Appendix 3 for full definitions):
    - Postoperative pulmonary complications (PPC)
    - Respiratory failure
    - Paralytic ileus
    - Incisional surgical site infection
    - Rectus sheath catheter/infusion-related complications
- Time to tracheal extubation in days
- Time to return of bowel function
- Time to first mobilisation
- Pain intensity at rest and on movement on each of postoperative days 1-5
- Postoperative opioid use in the first five days from the end of surgery
- Mortality at 30 and 90 days
- Chronic postoperative pain (Brief Pain Inventory (7) at 3 and 6 months)
- Health related quality of life (EQ5D-5L at 3 days, 3 and 6 months)
- Return to work and activity (Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) at 3 and 6 months)

3.2.2 Process measures

- Duration of postoperative hospital stay (number of days from randomisation until hospital discharge)
- Duration of postoperative stay in a level 2 or a level 3 critical care bed (from randomisation until discharge)
- Primary and secondary NHS care resource use (at 3 and 6 months)

For the definitions of care levels, see: Appendix 1

3.2.3 Health economic endpoints

- NHS costs of care within 6 months

- Productivity and informal care (i.e. unpaid care provided by family/friends) costs within 6 months
- Quality Adjusted Life Years (QALYs) over 6 months

3.3 Assessment of primary and secondary outcomes

OBAS is a patient-reported composite endpoint of pain scores, opioid side-effects, and patient satisfaction (range 0 [best] to 28 [worst] – see: Table 1). It was validated for use in perioperative trials and has good completion rates in similar patient groups (5,6,8).

Table 1: OBAS questionnaire. Total score = (sum of items 1-6) + (4 – score for item 7). Lower OBAS score indicates higher benefit

1. Please rate your current pain at rest on a scale between 0 (minimal pain) and 4 (maximum imaginable pain)
2. Please grade any distress and bother from vomiting in the past 24 h (0=not at all to 4=very much)
3. Please grade any distress and bother from itching in the past 24 h (0=not at all to 4=very much)
4. Please grade any distress and bother from sweating in the past 24 h (0=not at all to 4=very much)
5. Please grade any distress and bother from freezing in the past 24 h (0=not at all to 4=very much)
6. Please grade any distress and bother from dizziness in the past 24 h (0=not at all to 4=very much)
7. How satisfied are you with your pain treatment during the past 24 h (0=not at all to 4=very much)

"Postoperative days" on which OBAS and rest/movement pain are assessed are defined as follows: the calendar day on which surgery ends (defined as the end of surgical closure) will be taken as day 0. The calendar day after this is postoperative day 1, and so on. The time of day at which these are assessed will not be stipulated. Subsequent assessments should be as close as possible to 24 hours after the previous day's assessment. OBAS and rest/movement pain will be recorded at the same time.

Postoperative complications will be measured by review of medical records in line with the definitions in Appendix 3. The medical records of the index hospital admission will be reviewed for all patients. Following discharge after the index surgery, patients will be asked about hospital readmissions at the 3- and 6-month follow-ups. If there has been a hospital readmission within 30-days of randomisation the medical notes will again be reviewed to assess whether any events met the definition of a postoperative complication.

Time to return of bowel function will be measured using the GI-3 score (9), a composite endpoint defined as the achievement of both of the following two events: tolerating diet without significant nausea or vomiting for three consecutive meals; AND passage of flatus OR stool.

Pain intensity at rest and on movement on postoperative days 1-5 will be measured using a 10-point numerical rating scale.

Postoperative opioid administration will be collected as raw data by sites for the period from the end of surgery until 5 days (120 hours) later. This will be converted centrally, and without knowledge of group allocation, to oral morphine equivalents.

Chronic postoperative pain will be measured through the Brief Pain Inventory (7) at 3 and 6 months.

Days Alive and Out of Hospital at 30 and 90 days (10) will be derived and reported to allow future evidence syntheses.

Patient consent materials will allow for future data sharing and linkage (e.g. NELA, routine NHS datasets). 3- and 6-month time points are research follow-ups.

4 Plan of Investigation

4.1 Trial Schema – Figure 1

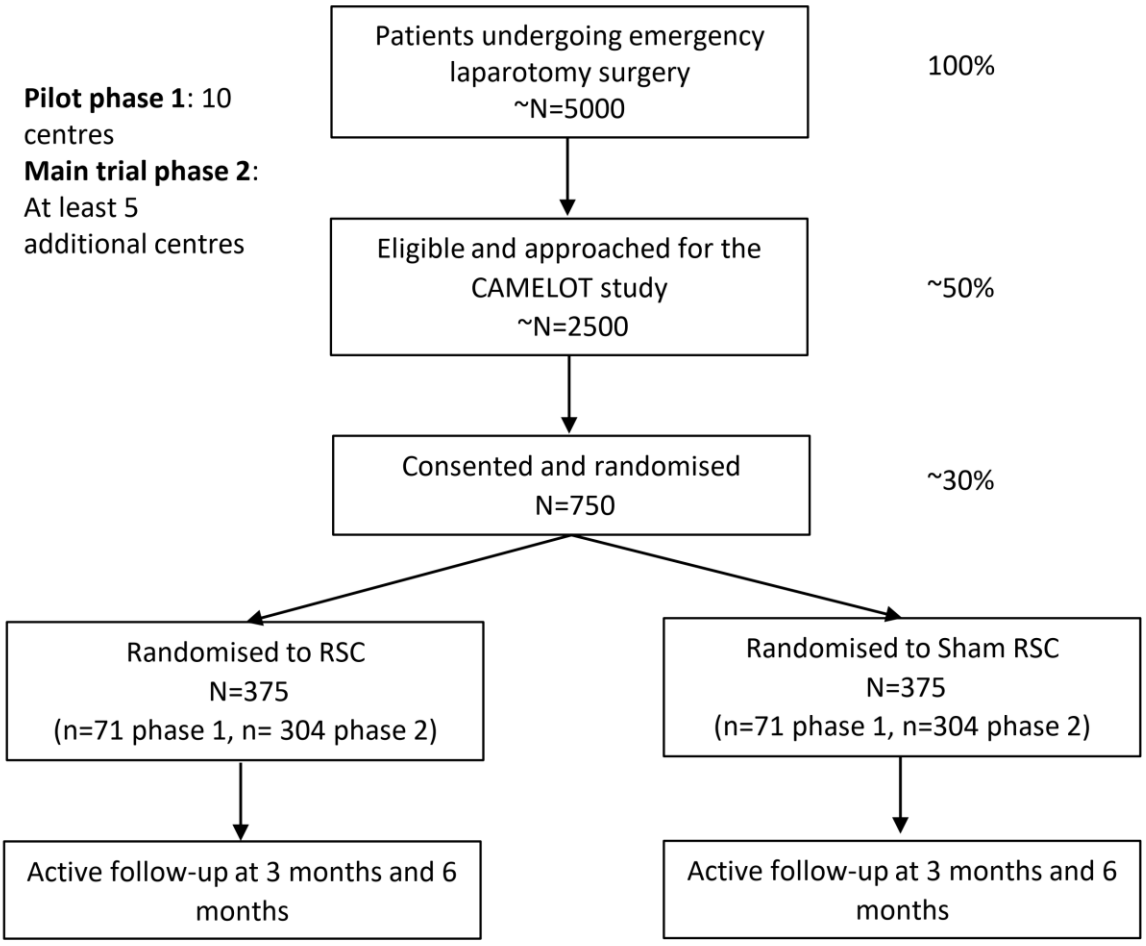


Figure 1 - Study designed with an internal pilot: progression from Phase 1 (12m recruitment) to Phase 2 (24m recruitment) dependent on achieving adequate recruitment.

4.2 Trial Design

Multicentre, pragmatic, parallel group, randomised controlled trial (RCT) conducted in NHS hospitals, with patient and outcome assessor blinding.

4.3 Trial Setting

Patients will be recruited from acute surgical services of at least 15 UK NHS hospitals.

4.4 Inclusion Criteria

- Age 18 years or over
- Undergoing surgery that:
  - would be eligible for inclusion in NELA* and
  - involves a midline laparotomy incision

4.5 Exclusion criteria

- Planned epidural anaesthesia
- Clinician refusal
- Lack of mental capacity to consent to trial participation
- Contraindications to RSC including allergy to local anaesthetic (LA), anatomical factors making RSC insertion impossible
- Existing co-enrolment in another clinical study if: i) the intervention in the other study is expected to influence the primary outcome (this will be considered by a senior clinician on a case-by-case basis); ii) it is considered too burdensome for the patient; or iii) it is not permitted by the other study
- Previous enrolment in the CAMELOT trial

*NELA is commissioned in England and Wales and enrols adults who undergo a non-elective abdominal procedure on the gastrointestinal tract. It includes all emergency gastrointestinal procedures on the stomach, large and small bowel, for conditions such as perforation, bleeding, abdominal abscess or obstruction, via open and laparoscopic approaches. This includes procedures required for complications of planned gastrointestinal surgery. Key exclusions include vascular, gynaecology, renal and trauma emergency surgery. 90% of NELA patients require a midline laparotomy and can be considered for inclusion.

The term “emergency” laparotomy is defined in line with NELA and the National Confidential Enquiry into Peri-Operative Deaths (NCEPOD) 2004, to encompass the following categories: “immediate” surgery (required within two hours of the decision to operate), “urgent” surgery (required within 2-18 hours of the decision to operate) and “expedited” surgery (required within days of the decision to operate).

A full list of NELA procedural inclusion / exclusion criteria is included in Appendix 2 and is also available at https://www.nela.org.uk/Criteria. During the course of the trial the NELA Project Team may make minor modifications to the definitions of surgical cases included within the audit. In this circumstance the inclusion/exclusion criteria for CAMELOT will be amended to ensure consistency with NELA. Although hospitals in Scotland/Northern Ireland (NI) are not participating in the NELA program, the same procedural eligibility criteria will be used.

4.6 Internal pilot

CAMELOT will incorporate an internal pilot in order to confirm predicted site enrolment, participant recruitment, compliance with the trial protocol and completeness of the primary outcome data. The duration of the internal pilot will be the first 12 months of recruitment. During this time, it is anticipated that 10 sites will be activated and at least 143 participants will have been randomised. Recruitment to CAMELOT will continue during the internal pilot analysis. A report will be compiled at the end of the internal pilot phase, which will be discussed at a monitoring meeting with the funder. Patients from the internal pilot will be

included in the final analysis. All participants from both phases will be followed up for 6 months post-randomisation.

4.6.1 Progression criteria for the main phase (phase 2)

The internal pilot will monitor 1) recruitment rates (proportion of screened patients that are eligible, eligible patients consented and randomised per site per month); 2) adherence to the allocated treatment and 3) primary outcome data completeness. If the trial proceeds to phase 2, patients from phase 1 will be included in the final analysis. Criteria for progression from phase 1 to phase 2 are outlined in Table 2.

These targets allow for staggered site opening. If all criteria are green, we will proceed to a full trial with the same protocol; if one or more criteria are amber, we will propose adaptions to address the short fall; if one or more criteria are red, we will discuss with the Trial Steering Committee (TSC) and funder whether the full trial is feasible. The results from the internal pilot will be central to an Investigators' meeting held after the first year to share best recruiting practices.

Criterion	Target	Green	Amber	Red
Participant recruitment	143	>140	115-139	<115
Centres open	10	10	8-9	<8
Randomisation rate/centre/month	2	≥1.9	1.5-1.9	<1.5
Adherence to allocated intervention	100%	≥95%	90-94%	<90%
Primary outcome data available	90%	≥90%	80-90%	<80%

Table 2: Progression criteria (after 12 months of active recruitment)

5 Trial Procedures

5.1 Recruitment and screening

Potential participants will be screened by clinical and research staff at the site having been identified from operating theatre lists and by communication with the relevant nursing and medical staff.

Data from NELA has allowed us to accurately map care pathways for this patient group across the UK. Ninety-four percent of patients are admitted to hospital as an emergency, with the remainder requiring emergency laparotomy for a complication of a previous elective surgical procedure within the same admission. Following surgical review, a decision to operate is made, which may be supported by investigations including computed tomography scan, serial clinical review, and an estimation of postoperative risk. Interventions during this time may include analgesia, intravenous fluid and antibiotics. The time between the decision to operate and arrival in theatre is the primary opportunity for screening and recruiting patients to CAMELOT. Most patients need surgery within an "urgent" timeframe (within 2-18 hours of decision to operate), with smaller numbers requiring "immediate" (<2 hours; 11% of NELA patients) or "expedited" surgery (18-24 hours; 17% of NELA patients).

Having identified eligible participants at sites, research team members will assess whether the patient is capable of giving consent to trial participation.

5.2 Informed consent

Patients awaiting emergency surgery may be affected by distressing symptoms of pain or vomiting and/or be under the influence of opioid analgesics. They may also have been given a lot of clinical information in a short time frame. Patients will only be approached if they are considered to have capacity to consider participation in the trial.

A layered consent process will be used. Patients will be approached by an authorised member of the local research team (as specified in the delegation log) and given a verbal description of the aims, methods, anticipated benefits and potential hazards of the trial, along with a brief information leaflet. The research team member will explain that they are free to decline to enter the trial or to withdraw at any time during the trial, for any reason. Within the time available before surgery, the patient will be given as much time as they request to spend deliberating. Before surgery, they will verbally signal their consent to participate in the trial and this will be documented in their medical notes and CRF.

For patients in Scotland, the verbal consent process must be witnessed throughout, with a name and signature provided for both the staff member receiving consent and the witness. In Scotland only, during the verbal consent process, the researcher will; i) ask the participant if they would be happy to remain in the trial should they go on to lose capacity and document their decision, ii) inform the participant that, if they choose not to remain in the trial, data will be retained up to the point of them losing capacity, and iii) inform the participant that a Welfare Guardian/Attorney or Nearest Relative will be informed that consent to remain in the trial should capacity be lost has been asked for and given (as applicable).

For a minority of patients there may be more time available before surgery and the patient may be free of distressing symptoms. In these cases, the research team member will offer the patient the choice of reading a full Patient Information Sheet, and providing written informed consent before or after surgery.

Following recovery from surgery, participants who gave only verbal consent before surgery, will be given a detailed Patient Information Sheet and asked to provide written consent for their ongoing participation in the trial. This will take place no sooner than the first postoperative day after surgery and within three days after surgery, unless there is a documented reason to deviate from this. The participant must be considered to have mental capacity to consider ongoing trial participation.

If it becomes apparent that the patient will not regain mental capacity to confirm consent within three days after surgery, then we will seek agreement or consent for ongoing participation under the Mental Capacity Act (in England, Wales or Northern Ireland) or Adults with Incapacity Act (Scotland) respectively. In England, Wales and Northern Ireland an authorised research team member (as specified on the delegation log) will approach a relative, friend or an independent clinician and ensure they are able and willing to act as a consultee, i.e. to advise on the participant's presumed wishes in relation to the trial. They will be provided with a detailed 'Consultee Information Leaflet' and a verbal explanation of the trial, and be given the opportunity to ask questions. If the consultee agrees on the participant's behalf, the consultee will be asked to sign a written 'Consultee Declaration Form'. If the consultee declines, this will be treated as a trial withdrawal with data collected to that point retained. In Scotland, providing that the participant has provided their verbal

consent to it, an authorised research team member will approach a Welfare Guardian/Attorney or Nearest Relative to inform them that the participant has agreed to remain in the trial should they go on to lose capacity. The patients original verbal consent should be respected. However, their legal representative can request to withdraw the participant from the trial; this request should be considered carefully to ensure that it reflects the wishes of the person before they lost capacity and the current situation. In all nations, discussions about trial participation with consultees/guardians/welfare attorneys/nearest relatives can be held in person or by telephone.

Should the patient regain capacity at a later time then confirmatory consent will be sought. If ongoing participation is declined, this will be treated as a trial withdrawal with data collected to that point retained.

5.3 Randomisation

Randomisation will take place after verbal consent has been given, baseline assessments have been completed and eligibility has been confirmed by the Principal Investigator, or a delegated medically qualified doctor, research nurse/practitioner or Advanced Nurse Practitioner who has undergone suitable training by an authorised member of the research team and is named on the delegation log.

Participants will be randomised after the midline incision has been performed and before the start of surgical closure, using a secure internet-based randomisation system ensuring allocation concealment.

Participants will be allocated in a 1:1 ratio to either RSC or sham RSC. The allocation will be computer-generated, stratified by centre and allocated with blocks of varying size.

5.4 Trial Treatment

Eligible patients will be randomised to receive either RSCs or sham (inactive) RSCs. The trial treatment will commence at the end of surgery, when the RSCs or inactive catheter will be placed during surgical incision closure, and continue for a target of 72 hours after the completion of surgery (maximum permitted: 5 days). Perioperative management for all patients during the trial treatment period will be in accordance with the recommended guidance below. If participants no longer wish to receive the trial intervention, their care will revert to standard care at the discretion of their clinical team.

5.4.1 Care for ALL participants

Care for all patients has been loosely defined, to remain pragmatic and reflective of the natural heterogeneity of clinical management, while avoiding extremes of practice. Participants in BOTH GROUPS will be given standard analgesia including opioid-based patient-controlled analgesia (PCA) in addition to the RSC/sham RSC. The non-RSC elements of analgesia (e.g. choice of PCA drug, paracetamol, non-steroidal anti-inflammatories, intravenous magnesium) will be specified by the attending anaesthetist before randomisation. All other patient care will be conducted as per routine practice. RSC/sham will be removed 72 hours after surgery unless there is a documented reason to deviate e.g. clinical team assessment that pain cannot yet be controlled by oral analgesia alone. The maximum permitted duration of RSC use is 5 days. Duration of RSC use will be recorded.

Perioperative epidural analgesia will not be permitted, as epidural infusion combined with RSC infusion would risk toxic systemic levels of LA. Planned epidural analgesia is therefore

an exclusion criterion. Other aspects of care will be in line with current best evidence and defined standards.

5.4.2 Intervention group

Insertion of RSCs with infusion of local anaesthetic (LA) for 72 hours from the end of surgery in accordance with the study manual. Two RSCs will be inserted by the operating surgeon using a standardised technique at the end of surgery, including an initial bolus of LA. The LA infusion device will be connected and concealed in opaque packaging to maintain patient and outcome assessor blinding. The specific LA infused will not be mandated; each hospital will choose from a recommended list of equipotent alternatives in routine clinical use for nerve block catheter infusions (e.g. 0.125% levobupivacaine, 0.1% bupivacaine, 0.2% ropivacaine). The choice of LA, mode of delivery via either automated bolus or constant infusion regime, and total infusion will be documented. The infusion device will be chosen by each hospital from a recommended list provided in the study manual and will be set to deliver either a constant infusion of LA or intermittent boluses, as per the hospital team's preference. The LA delivery device and mode will be documented. This will ensure the trial remains pragmatic and reflects current NHS practice.

5.4.3 Comparator group

Comparator group participants will be allocated sham RSCs with inactive infusion device in place for 72 hours from the end of surgery in accordance with the study manual. At the end of surgery two shortened sham RSCs will be fixed onto the skin surface (NOT inserted into the skin/muscles) using the same adhesive dressings as the intervention group and attached to an inactive infusion device concealed in opaque packaging.

5.4.4 Duration of RSCs or sham RSCs

In both groups, the RSCs or sham RSCs will by default be removed at a suitable opportunity after 72 hours have elapsed since the end of surgery, unless there is a documented reason to deviate (maximum permitted duration: 5 days). Ward-based clinical teams responsible for postoperative care may request removal of the RCS/sham RCS earlier if there is a suspected complication of the catheter e.g. infection, leakage or malfunction. Conversely, they may request that they are kept in place for longer (maximum duration: 5 days) if they assess that a patient's analgesia would be inadequate if stopped at 72 hours after surgery. Both these situations should be discussed with the research team, including the local PI. Reasons for variation will be captured on the study case report form (CRF).

5.5 Blinding and procedures to minimise bias

To minimise bias, patients and research nurses involved with data collection will be blinded to group allocation through the use of sham RSC in the comparator group and concealment of the local anaesthetic infusion devices in opaque packaging. Patients will be made aware before entering the study that they will not be told which treatment they will receive.

Clinical staff responsible for administering patient medication will be allowed to temporarily remove the opaque packaging as required to re-fill and check LA infusions in line with usual clinical care. They will be informed of group allocation by unblinded research team members. They will be instructed not to reveal the allocation or the contents of the opaque packaging to the patient during these interventions, or to blinded research staff. A similar technique has been used successfully in a previous trial (11).

It is not possible to blind anaesthetists or surgeons from the theatre team, but they will not be involved in outcome data collection. They will also be instructed not to reveal the group allocation to the patient or research staff. To encourage good adjunct analgesia as standard for all patients, anaesthetists will be asked to specify non-opioid analgesics prior to randomisation, i.e., without knowledge of group allocation. All intra- and postoperative analgesia administered will be recorded. Research nurses responsible for data collection and participant follow-up will not randomise patients and will not be in the operating theatre on the day of surgery.

The success of blinding will be assessed using the Bang Blinding Index after removal of the RSCs or sham RSC (12).

Other measures will be taken to minimise bias. Selection/allocation bias will be prevented by centralised randomisation with allocation sequence concealment. Performance bias will be minimised by the blinding methods described. Through the use of sham catheters and concealed infusion devices, medical staff members on the ward will not be immediately aware of participant group allocation. The patient consent process will describe the uncertainty about the efficacy of RSCs. Therefore, participants should not have a strong expectation that any one method will lead to a more favourable result. Detection bias will be minimised by blinding participants and outcome assessors and using outcome measures that are defined as far as possible on the basis of objective criteria. Attrition bias will be minimised by using established methods developed in the Bristol Trials Centre (BTC) to maximise the quality and completeness of the data, for example regular monitoring of data, automated data queries in the study database, offering alternative methods for participating in follow-up (e.g., postal, online or telephone). Data will be analysed by intention-to-treat with every effort made to include all randomised participants. Reporting bias will be minimised by pre-specifying study outcomes and following a detailed analysis plan which will be prepared in advance of any comparative analyses of the study data.

5.5.1 Unblinding

5.5.1.1 Accidental unblinding

The impact of accidental unblinding should be minimised. For example, participants will be instructed that if they feel that they have become aware of their trial group allocation, they should not reveal this to research staff. If research staff members become unblinded, they should not communicate group allocation to the participant.

5.5.1.2 Emergency unblinding

Requests to unblind on clinical grounds, e.g. to treat a complication, are not anticipated. However, if unblinding is requested on safety grounds, where knowledge of the allocation would alter management of an adverse event, this will be facilitated. Working instructions will be provided to sites with guidance on unblinding procedures. . Where appropriate and feasible, all care shall be taken to ensure that outcome assessors within the hospital study team and the patient remain blinded. Emergency unblinding requests will be fully documented including who requested the unblinding and the reason for unblinding.

Unblinding rates will be monitored throughout the trial by the study team and by the independent Data Monitoring and Safety Committee (DMSC) that will be established to oversee participant safety in the trial.

5.5.1.3 OBAS score collection by unblinded assessor

In exceptional circumstances (e.g. out of hours and no blinded research staff available), it is acceptable for the OBAS to be collected by an unblinded assessor. This will support a high rate of primary outcome completion without necessarily biasing its reporting. OBAS is a patient-reported measure, with questions posed by a member of research staff, rather than a measurement conducted by a member of research staff. If the score is collected by an unblinded assessor, this must be recorded on the trial CRF along with a reason. The unblinded assessor should not reveal group allocation to the patient. Rates of unblinded assessor OBAS data collection will be monitored throughout by the trial team, on both an overall and site-specific basis, and reported to trial oversight committees.

5.6 Data Collection

Each patient will be assigned a unique study ID number. All data recorded on paper relating to the participant will be located in CRF folders, which will be stored securely at site. Staff with authorisation to make changes to the study records, including the study database, will be listed on the study delegation log.

The primary data source will be the participant's medical notes and questionnaires, alongside the data collection forms for the study, which will be inputted on the online trial database.

Data collection and entry will be organised based on blinded/unblinded status, with database section access dependent on role. Unblinded research staff will collect data such as LA type and dosage, whereas blinded research staff will deal with baseline demographics and postoperative outcomes.

Screening data will be collected for all patients undergoing emergency laparotomy surgery via midline incision. Age, sex and Index of Multiple Deprivation (IMD) will be collected for all patients irrespective of whether they decide to participate. This information is collected to assess any difference in the patients that do not take part compared to patients that do, to establish if there are any socioeconomic barriers to participation.

Baseline data will be collected after verbal consent has been given before surgery.

After surgery and while in hospital, participants will be visited once a day for five days by research staff, who will administer a brief questionnaire (OBAS) asking about pain and other symptoms, and have their medical notes reviewed.

Patients will be contacted via email or telephone to complete a short questionnaire on chronic pain, health-related quality of life, return to work/activities and resource use at 3 and 6 months post-randomisation. We will ask the local research teams a week before follow-up to check the patient is still alive.

Data collection will include the following elements:

a) A screening log of all patients undergoing emergency laparotomy surgery via midline incision, including age, sex and Index of Multiple Deprivation (IMD) for place of residence derived from the patient's residential postcode, as recorded in their hospital records.
b) Patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility.
c) Consent information collected prior to randomisation for all participating patients.

d) Baseline information (e.g. medical history and verbal consent)
e) Randomisation details will be collected for all patients who wish to continue into the trial.
f) Operative and anaesthetic details collected for patients randomised.
g) Data relating to surgery and hospital stay collected for all participating patients.
h) Data on acute post-operative pain (measured via Numerical rating score (NRS)), persistent post-surgical pain (measured via the Brief Pain Inventory (BPI)), adverse events, health status questionnaires, healthcare resource use, and return to work/activity collected during the hospital stay and at 3 and 6 months post randomisation.
i) Assessment and reporting of any SAEs experienced, from randomisation to 6 months post-randomisation.

An overview of the data collection is shown in Table 3.

Reasons for non-completion of any assessment will be recorded and coded, where possible. Missing items or errors on the questionnaire will be dealt with according to the scoring manual via imputation methods. Adherence rates will be reported in results, including the numbers of patients who have withdrawn from the study, have been lost to follow up or died. Causes of death for patients who die will be recorded.

Table 3 Summary of Data collection

Data Collection	Baseline	Intraoperative	Post-end of surgery (Days)					Discharge	Post randomisation (Months)	
			1	2	3	4	5		3	6
Verbal consent	✓									
Randomisation		✓								
Written consent			→							
Demography	✓									
Operative and anaesthetic details		✓								
OBAS			✓	✓	✓	✓	✓			
Post-operative complications			✓	✓	✓	✓	✓	✓	✓	
Time to return of bowel function			✓	✓	✓	✓	✓	✓		
Time to 1st mobilisation			✓	✓	✓	✓	✓	✓		
Pain at rest and on movement			✓	✓	✓	✓	✓			
Postoperative opioid use			✓	✓	✓	✓	✓			
Length ICU stay								✓		
Length of hospital stay								✓		
Bang blinding index								✓		
HRQoL (EQ5D-5L)					✓				✓	✓
Vital status								✓	✓	✓
Chronic postoperative pain (BPI)									✓	✓
Serious adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓
Resource use (CRF and, at 3 & 6 months, patient questionnaire)		✓						✓	✓	✓
Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)									✓	✓

5.7 Predefined protocol deviations

- Failure to insert RSCs in an intervention group patient
- Maintaining RSC catheter placement and LA infusion for less than 24 hours or more than 5 days in an intervention patient
- Placement of real RSC or other abdominal regional local anaesthetic block (e.g. rectus sheath or transversus abdominal plane block) in a control group patient
- Maintaining sham catheters and inactive infusion device in place for less than 24 hours or more than 5 days in a control group patient

All major protocol deviations (i.e. those affecting patient safety and/or data integrity, and those relating to consent procedures) are to be reported individually using the Sponsor

Protocol Deviation Assessment Report Form and sent to the Sponsor, Cc. to the trial management team. If the Sponsor deems that the event constitutes a serious breach, an additional Sponsor Serious Breach Notification Form must be completed within 24 hours.

Minor protocol deviations are to be recorded using the Sponsor Protocol Deviation Log, which should be provided to Sponsor on a monthly basis.

The following are **not** classified as protocol deviations:

- Instillation of LA around the surgical wound at the end of surgery for a control group patient
- Spinal (intrathecal) LA or opioid placement for either intervention or control group patients

It is recommended to maintain RSC LA or sham setup placement for 72 hours after surgery, up to an absolute maximum of 5 days. The total duration, and reasons for any variance from 72 hours will be recorded, monitored and actively managed with sites throughout the trial.

5.8 Follow-up procedures

Data for the primary outcome and most secondary outcomes will be collected during hospital stay. Patients will be followed up at approximately 3 months and at 6 months post-randomisation for information on pain, adverse events, resource use and quality of life.

5.8.1 Likely rate of loss to follow-up

Until discharge from hospital following the index surgery, the only losses to follow-up will be due to death or a participant withdrawing. A minimum of one OBAS score by participants within the first five postoperative days can be used for the primary outcome. We expect all five OBAS assessments to be missed in no more than 10%, and have allowed for this when estimating our study sample size. For secondary outcome collection following hospital discharge, vital status and some aspects of resource use will be collected from routine local NHS records. For patient-reported outcomes, previous studies in this population suggest a 75-90% participation in follow-up at 3 and 6 months (13,14).

5.9 Change of participation

All participants are free to discontinue their participation in the study, or elements of it, at any time. A change may also be requested by a clinician, e.g. due to a safety event, following discussion with the site Principal Investigator.

A 'Change of Participation Status' form will be completed to document the request change and, where possible, the reason for this change. Data collected up to the point of the change request will be retained and included in study analyses.

5.10 Definition of end of trial

The trial will end for the participant after they have completed the six-month follow-up. The end of the trial as a whole will be when all participants have completed the six-month follow-up, or are lost to follow-up, all data queries have been resolved, the database has been locked and analyses completed.

The Data Monitoring and Safety Committee (DMSC) will monitor safety data throughout the trial. Based on these results, they may recommend termination of the trial on safety grounds. They will report any concerns to the Trial Steering Committee (TSC), who will inform the Sponsor and take appropriate action, which may include stopping the trial, to address

concerns about participant safety. The Research Ethics Committee will be informed in writing if the trial is suspended or terminated early.

6 Statistics

6.1 Sample size calculation

The sample size is 750 participants (375 per group), which will provide 90% power to detect a 15% relative reduction in mean OBAS assuming a standard deviation (on the logarithmic scale) of 0.65 (8), 5% statistical significance and allowing for 10% missing data (in line with previous surgical trials (6,8)). This target reduction in mean OBAS was ascertained through development work with clinicians and patients. Our national survey confirmed that >90% of clinicians would change their routine practice based on improvements in pain scores as a primary outcome. Three patient groups were consulted to inform this application, including the newly established NELA Patient Group. They all considered a 15% reduction in OBAS to be an important improvement in analgesia quality from the patient perspective.

A trial in 750 participants would also have 90% power to detect important differences in key secondary outcomes. In particular the study would have 90% power to detect a 30% relative reduction in delayed gut function at 3 days (assuming 40% delayed function in the comparator group), a 35% relative reduction in pulmonary complications (assuming 30% complication rate in the comparator group) and a 4-day reduction in the median length of stay (assuming a median stay of 15 days in the comparator group) (15,16).

6.2 Statistical analysis

Primary analyses will be by intention-to-treat (ITT) and will be directed by a pre-specified statistical analysis plan. Analyses will use data from all participants randomised. Results will be reported in accordance with the CONSORT guidelines.

The primary outcome will be analysed using regression. It is anticipated that the mean OBAS follows a log-normal distribution. Time-to-event outcomes will be analysed using survival methods and binary outcomes will be compared using generalised linear models. Quality of life scores will be compared using a mixed model. Interactions between treatment and time will be examined and, if significant at the 10% level, results will be reported separately for each post-operative time point; otherwise overall treatment effects will be reported. Mixed models allow all participants with data to be included in the analysis, i.e., partial missing data (assumed missing at random) is permitted. Adverse events will be described. Analyses will be adjusted for variables used to stratify the randomization (and baseline values if measured), with site fitted as a random effect.

Model validity will be checked using standard methods; if a model is a poor fit, alternative models or transformations will be explored. Outcomes analysed on a logarithmic scale will be transformed back to the original scale after analysis and results presented as geometric mean ratios. All analyses will use the sham as the reference group.

6.2.1 Subgroup analyses

We will conduct subgroup analysis of the primary outcome by:

- sex assigned at birth (male vs. female),
- and the use of spinal anaesthesia with opiates (yes vs. no).

Placement of spinal anaesthesia/analgesia occurs before randomisation so the clinical decision to use this will not be based on group allocation. We will describe the primary outcome in the subgroups and test for differences in the primary outcome between subgroups by including treatment by subgroup interaction terms in models.

6.2.2 Exploratory analysis

We will conduct an exploratory analysis comparing the primary outcome in those intervention participants receiving constant local anaesthetic infusion with those receiving automated intermittent local anaesthetic boluses.

6.2.3 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants. Safety data will be reported to the DMSC at a frequency to be agreed, together with any additional analyses the committee requests. In these reports, the data will be presented by group but the allocation will remain masked.

6.2.4 Criteria for the termination of the trial

The trial may be terminated early on the recommendation of the DMSC or the results of another study supersede the necessity for completion of this study.

6.3 Economic evaluation

The primary economic evaluation will take an NHS perspective and estimate the cost per quality adjusted life year (QALY – based on EQ5D-5L) and the incremental net benefit (at National Institute for Health and Care Excellence (NICE) cost-per-QALY thresholds) of RSC over the 6-month follow-up period. We will identify and measure economically relevant differences in the initial procedures (e.g. RSC device, surgeon/anaesthetist grade, procedure and recovery room time) on the CRF. Research-driven costs (e.g. placement of the sham) will be excluded. This information will be combined with national (where available) or local procurement unit costs to micro-cost the incremental cost of the initial procedure and inpatient stay. A brief patient-reported resource use questionnaire (17) will assess core items of NHS care (e.g. readmissions, primary care, pain medication) at 3 and 6 months from date of randomisation. In addition, participants will be asked about return to work/usual activities (Work Productivity and Activity Impairment Questionnaire: General Health, WPAI:GH (18)) and any informal care requirements. Responses will be combined with national unit costs to estimate the costs of care post-randomisation. Informal care by family, friends, and others will be valued using a shadow price method. QALYs will be estimated from EQ5D-5L responses post-operatively, and at 3 and 6 months from date of randomisation. Utility scores will be derived using the UK value set recommended by NICE at the time of analysis. QALYs will be estimated, assuming a common utility score at baseline, and adjusting for mortality observed during follow up using the area under the curve approach (19).

The economic analysis will take an intention to treat approach with imputation of missing data. In the primary economic analysis, we will estimate the cost per QALY gained of RSC at 6 months from the perspective of NHS. Based on NICE willingness to pay thresholds for a QALY (currently £20,000- £30,000) we will calculate net benefit statistics for each patient and use net benefit regressions, adjusting for stratification variables and baseline characteristics to estimate the incremental net benefit (and 95% CIs) and determine whether RSC is cost-effective. Uncertainty will be explored using cost effectiveness acceptability curves to estimate the probability that RSC is cost-effective at a range of plausible cost-effectiveness thresholds. In secondary analyses we will estimate the cost per improvement

in post-operative OBAS and take a broader perspective, including the incremental costs of informal care, and productivity losses after surgery. Further detail of the economic analyses will be published in a pre-specified health economic analysis plan.

7 Trial Management

7.1 Trial Oversight

7.1.1 Trial Management Group

The trial will be managed by a trial management group (TMG), which will meet face to face or by teleconference approximately every 6 weeks for the duration of the study. The TMG will be chaired by the lead applicants/Chief Investigator and will include representatives from Bristol Trials Centre (BTC). Other members of the research team will be invited to attend as required.

The TMG will be supported by BTC, which is a UK Clinical Research Collaboration registered Clinical Trials Unit. BTC will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and manage the trial on a day to day basis.

7.1.1.1 Day-to-day management

The study will be managed by the Chief Investigator (CI), with mentoring and support from senior members of the research team who will provide experience of implementing large scale clinical trials, and the Trial Manager, with full support from the wider BTC. The BTC has an established track record of designing, conducting, managing and reporting multi-centre clinical trials. The BTC has experience in building study database systems and providing randomisation services.

The CI and BTC team will work with the co-applicants to prepare the final protocol and submit the Research Ethics Committee (REC) and associated Health Research Authority (HRA) applications. The BTC will prepare the study manual, provide the randomisation service and design and implement the data management system.

The CI, BTC team and Sponsor (University Hospital Southampton NHS Foundation Trust) will endeavour to ensure that the trial runs according to the agreed timetable, recruitment targets are met, the CRFs are completed accurately, the trial complies with relevant ethical and other regulatory standards, and that all aspects of the study are performed to the highest quality. The CI and BTC team will also train investigators at participating centres (sites), check that centres are ready to start (“green light”) and monitor their progress during the trial. The Trial Manager will be the contact point to provide support and guidance to the participating centres throughout the study.

7.2 Monitoring of sites

7.2.1 Initiation visit

Before the study commences, training session(s) will be organised by the BTC. These sessions will ensure that personnel at each site involved fully understand the protocol, CRFs, the operational requirements of the study and the assessments to be conducted within the trial e.g. OBAS assessments.

7.2.2 Site Monitoring

BTC will carry out central monitoring and audit of compliance of centres/surgical specialties with the principles of Good Clinical Practice (GCP) and data collection procedures. The study database will have extensive in-built validation and the TMG will review the completeness and consistency of the data throughout the trial. BTC will not check CRFs against the data entered or against source data, unless there are good reasons to visit the site to complete a monitoring visit (e.g. the central monitoring highlights a problem). As this is a blinded study any misclassification errors should have minimal impact on the study results.

7.3 Trial Steering Committee and Data Monitoring and Safety Committee

An independent TSC will be established to oversee the conduct of the study. It is anticipated that the TSC will comprise the CI, an independent chair and at least two additional independent members, at least one of whom will be a patient/public representative. The TSC will develop terms of reference outlining their responsibilities and operational details. The TSC will meet before recruitment in the trial begins and then approximately every six months during the course of the study.

An independent DMSC will be established to review safety data during the course of the study and will advise on interim analyses. The DMSC will develop a charter outlining their responsibilities and operational details. The DMSC will meet jointly with the TSC, before recruitment in the trial begins and they will meet approximately every six months after recruitment has begun.

Stopping rules for the trial will be discussed at the first joint TSC/DMSC meeting, and decisions documented in the DMSC Charter.

8 Safety reporting

Serious and other adverse events will be recorded and reported in accordance with the Good Clinical Practice (GCP) guidelines and the Sponsor's Serious Adverse Event Recording and Reporting Standard Operating Procedure. Recording and reporting processes are reflective of the non-CTIMP status of CAMELOT.

8.1 Safety reporting definitions

Adverse Event: An AE is any untoward medical occurrence in a subject to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities.

Relatedness of AEs: An event may be considered by the reporting investigator, Chief Investigator or Sponsor to be related to a trial intervention if there is evidence or argument to suggest a causal relationship. If an AE is assessed as being "possibly", "probably" or "definitely" related to the trial intervention it becomes an adverse reaction (AR).

Seriousness of AE/ARs: If an AE/AR meets one of the following criteria it is defined as serious:

a) results in death,

b) is life-threatening,
c) requires hospitalisation or prolongation of existing hospitalisation,
d) results in persistent or significant disability or incapacity,
e) consists of a congenital anomaly or birth defect, or
f) is otherwise considered medically significant by the investigator.

Expectedness of AE/ARs: In emergency laparotomy surgery, a range of postoperative complications may be expected and occur quite frequently. Rectus sheath catheters are already in widespread clinical use and have a number of recognised potential complications that may also be expected.

8.1.1 Expected adverse events

Associated with emergency laparotomy surgery:

- Acute kidney injury
- Acute Respiratory Distress Syndrome (ARDS)
- Anaphylaxis
- Anastomotic breakdown
- Bowel infarction
- Cardiac arrhythmia
- Cardiac arrest
- Cardiogenic pulmonary oedema
- Deep vein thrombosis
- Delirium or acute psychosis
- Electrolyte imbalance
- Gastrointestinal or other postoperative bleed
- Infection, source uncertain
- Laboratory confirmed bloodstream infection
- Multi-organ dysfunction syndrome
- Myocardial infarction
- Myocardial injury
- Pneumonia
- Paralytic ileus
- Perforated viscus
- Postoperative haemorrhage
- Pulmonary embolism
- Stroke
- Surgical site infection (superficial, deep or organ/space)
- Urinary tract infection

Associated with rectus sheath catheter / local anaesthetic infusion:

- Surgical site infection (superficial or deep incisional)
- Catheter site bleeding or haematoma formation
- Catheter entrapment, dislodgement, breakage or blockage
- Nerve damage
- Local anaesthetic toxicity
- Anaphylaxis to local anaesthetic
- Skin reaction to catheter or adhesive dressing

8.2 Collecting and reporting AE/SAE data

Initial handling of reported SAEs will be delegated to BTC by the trial Sponsor.

8.2.1 AE/SAE collection and reporting – recruiting sites.

AEs will primarily be sought by reviewing patients and their records to see if one or more of the defined postoperative or intervention-related complications has occurred. If an event meets the criteria for a complication, its impact and required level of medical intervention will be graded (see Appendix 3). This will include reviewing whether the definition of an SAE has been met.

Non-serious AEs/ARs will be recorded as above on the trial CRF but do not require additional reporting to BTC or Sponsor.

If an AE meets the definition of an SAE, it should be reported to BTC within 24 hours of the local research team becoming aware of the event if it meets one of these criteria:

a) It is **fatal**, OR

b) It is both **related** (as defined above) **AND unexpected** (i.e. the type of event is not listed in the protocol as an expected occurrence). This second category constitutes a non-IMP SUSAR (suspected unexpected serious adverse reaction in a non-investigational medicinal product study).

All other SAEs will be recorded as above on the trial CRF but do not require additional reporting to BTC or Sponsor.

8.2.2 SAE reporting by BTC and Chief Investigator

Non-IMP SUSAR reports should be made to BTC within 24 hours of the local research team becoming aware of the event. The report will be reviewed by the Chief Investigator (or delegate). If the event meets the criteria for a related and unexpected SAE, they will be reported to the Sponsor (within 24 hours of the BTC being made aware) and the REC within 15 days from receipt of the report.

Data on all AEs will be reported regularly to the DMSC and Sponsor for review.

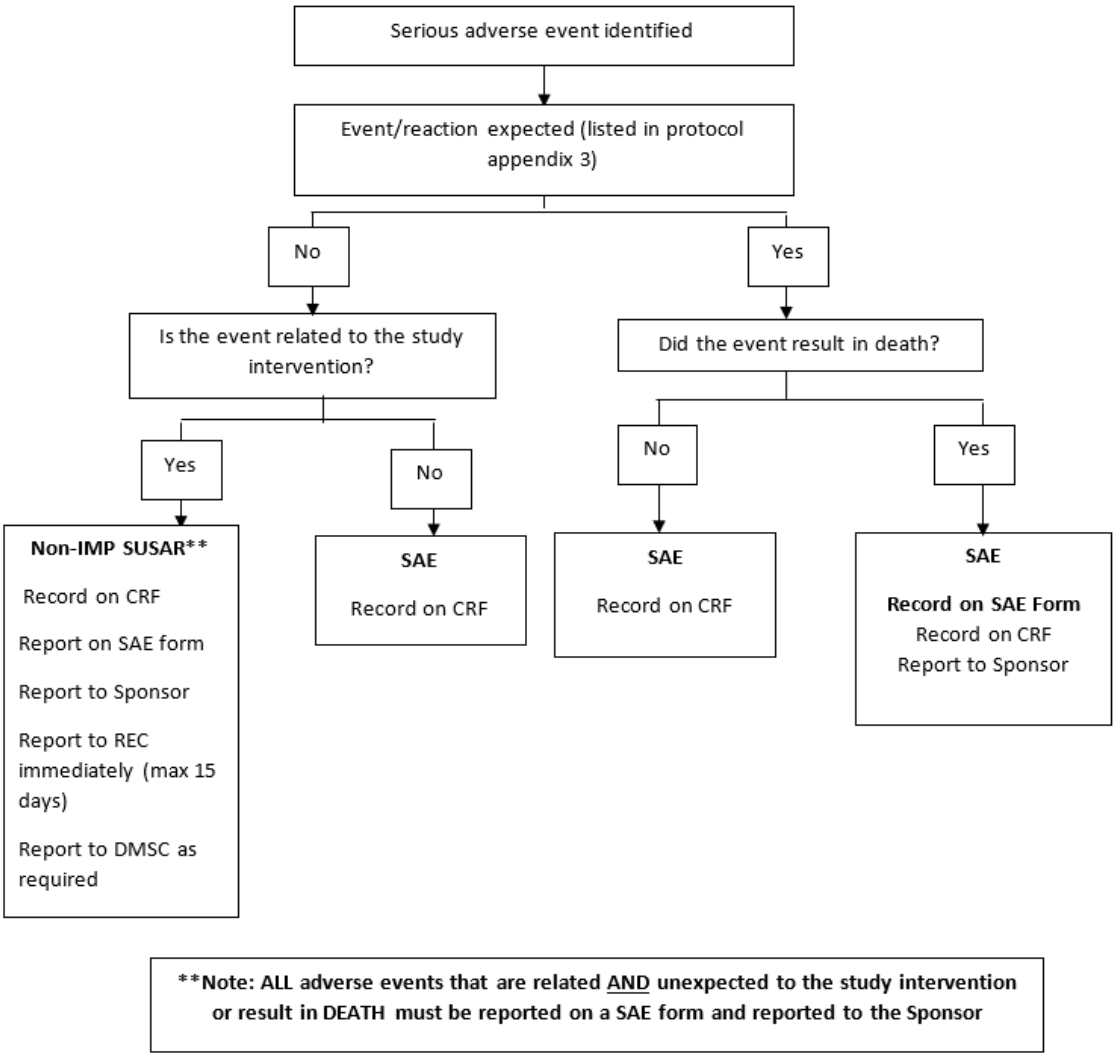
8.3 Period for recording serious adverse events

Data on adverse events will be collected from insertion of the rectus sheath catheter and for the duration of the participant's post-operative hospital stay. Thereafter only SAEs and AEs of interest will be recorded for the 6-month follow-up period. Expedited reporting of fatal SAEs and non-IMP SUSARs to the Sponsor **will not** be required after the patient has been discharged from the primary hospital admission.

8.4 Urgent safety measures

The CI will take urgent safety measures to ensure the safety and protection of trial participants from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the Sponsor and REC of this event in writing, setting out the reasons for the urgent safety measures and the plan for further action, within three days. The Sponsor must be sent a copy of the correspondence with regards to this matter.

Figure 2 - Serious adverse event reporting flow chart



9 Ethical considerations

9.1 Review by an NHS Research Ethics Committee

The research will be performed subject to a favourable opinion from an NHS REC and Health Research Authority (HRA) and local site capacity and capability confirmation. Ethics review of the protocol for the trial and other trial related essential documents (e.g. Patient Information Leaflet (PIL) and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

9.2 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL.

9.3 Co-enrolment

Co-enrolment to other observational and interventional trials is encouraged as long as any other trial interventions do not have a similar biological mechanism, nor seek to modify the same primary outcome. Local research teams should consider any additional burden that may be placed on patients by inviting them to participate in multiple studies. Co-enrolment will be agreed on a trial by trial basis.

The TMG have agreed that co-enrolment with FLO-ELA (Fluid Optimisation in Emergency Laparotomy Trial, ISRCTN14729158) is acceptable, as both trials place minimal burden on the participant.

9.4 Expenses

There will be no “research only” visits, as follow-up data collection will occur via telephone or online questionnaire, therefore participant travel expenses are not required.

10 Research governance

This study will be conducted in accordance with:

- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- Research Governance Framework for Health and Social Care

10.1 Sponsor approval

Any amendments to the trial documents must be approved by the Sponsor, TSC and funder prior to submission to the HRA/REC.

10.2 NHS confirmation of capacity and capability

Confirmation of capacity and capability is required from each participating site prior to their participation in the trial.

Any amendments to the trial documents approved by the REC and HRA and MHRA will be submitted to participating sites for information and implementation, as required.

10.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents that they receive and ensure that the changes are complied with.

10.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor’s policy, which is consistent with the Research Governance Framework. All study related documents will be

made available on request for monitoring and audit by BTC, the Sponsor, the relevant REC and for inspection by other licensing bodies.

10.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

10.6 Clinical Trial Authorisation

The study intervention is not classed as an investigational medicinal product and a Clinical Trial Authorisation from the MHRA is not required.

11 Data protection and participant confidentiality

11.1 Data protection

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act (UK), NHS Caldicott Principles (UK), The Research Governance Framework for Health and Social Care (UK), and the conditions of Research Ethics Committee Approval, or corresponding legislation or approvals for a particular participating site. Personal data recorded on all documents will be regarded as confidential. The PI must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The PI must ensure the patient's confidentiality is maintained at all times. The Sponsor will ensure that all participating partner organisations will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the trial management team will require access to patient notes for quality assurance purposes and source data verification, but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected.

11.2 Data handling, storage and sharing

11.2.1 Data handling

Data will be entered onto a purpose designed database, and data validation and cleaning will be carried out throughout the trial. Standard operating procedures (SOPs) for database use, data validation and data cleaning will be available and regularly maintained.

Data will be submitted to the Bristol Trials Centre directly into the password protected database and maintained on a SQL Server database system within the University of Bristol which will only be accessible to relevant members of the research team.

11.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years (non-CTIMP) after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where trial related information is

documented in the medical records, these records will be identified by a label bearing the name and duration of the trial in accordance to Sponsor policy.

Data will be kept at the University of Bristol (and/or Sites) for this time and, at the end of the archiving period, will be destroyed by confidential means with the exception of a final trial dataset which will be made available for data-sharing purposes (see Section 11.2.3). Data held at the University of Bristol will conform to the University of Bristol Data Security Policy and in Compliance with the General Data Protection Regulation (GDPR) as it applies in the UK, tailored by the Data Protection Act 2018. A secure electronic 'key' with a unique participant identifier, and key personal identifiers (e.g. name, date of birth and NHS number) will also be held indefinitely, but in a separate file and in a physically different location (University of Bristol server behind a firewall). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

11.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be retained for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body. Patient identifiers would not be passed on to any third party.

12 Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available.

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14 Amendments

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
Amendment 1	1.0	01 July 2022	2.0	12 April 2023	Trial team personnel changes, OBAS by unblinded assessor in exceptional circumstances, clarification of Scottish recruitment processes, data storage changes, minor corrections and clarifications throughout	02/05/2023

15 Appendices

15.1 Appendix 1 - Level of care after surgery

The level of care should be defined according to the care the patient received rather than the location. For example, a patient receiving level 2 care in a level 3 area should be recorded as receiving level 2 care.

1. Critical care level 3: includes advanced organ support e.g. invasive ventilation, renal replacement therapy.
2. Critical care level 2: may include advanced cardiorespiratory monitoring (e.g. invasive arterial / central venous monitoring) and basic organ support (e.g. non-invasive ventilation, inotropic/vasoactive drug administration).
3. Post-anaesthetic care unit: care within a designated area for the patients in the immediate recovery from anaesthesia. May deliver care at levels 1 to 3.

Surgical ward (level 0/1): normal ward care without level 2 or 3 capabilities.

15.2 Appendix 2 – NELA procedural inclusion/exclusion criteria

(from NELA specification V1.8 05/11/2021)

NELA Inclusion Criteria

NELA will enrol the patients treated in England or Wales who meet the following criteria:

- aged 18 years and over,
- who undergo an expedited, urgent or emergency (NCEPOD definitions) abdominal procedure on the gastrointestinal tract.
- This will include
- Open, laparoscopic, or laparoscopically-assisted procedures*
- Procedures involving the stomach, small or large bowel, or rectum for conditions such as perforation, ischaemia, abdominal abscess, bleeding or obstruction
- Washout/evacuation of intra-peritoneal abscess (unless due to appendicitis or cholecystitis – excluded, see below)
- Washout/evacuation of intra-peritoneal haematoma
- Bowel resection/repair due to incarcerated incisional, umbilical, inguinal and femoral hernias (but not hernia repair without bowel resection/repair). E.g. Large incisional hernia repair with bowel resection
- Bowel resection/repair due to obstructing/incarcerated incisional hernias provided the presentation and findings were acute. This will include large incisional hernia repair with division of adhesions.
- Laparotomy/laparoscopy with inoperable pathology (e.g. peritoneal/hepatic metastases) where the intention was to perform a definitive procedure. This does not include purely diagnostic procedures.
- Laparoscopic/Open Adhesiolysis
- Return to theatre for repair of substantial dehiscence of major abdominal wound (i.e. “burst abdomen”)
- Return to theatre for complications that require the assistance of a general surgeon following gynaecological oncology surgery.
- Any reoperation/return to theatre for complications of elective general/upper GI surgery meeting the criteria above is included. Returns to theatre (apart from those gynaecology-oncology complications described immediately above this point), for complications following non-GI surgery are excluded (see exclusion criteria below).
- If multiple procedures are performed on different anatomical sites within the abdominal/pelvic cavity, the patient would be included if the major procedure is general surgical. E.g.
- Non-elective colonic resection with hysterectomy for a fistulating colonic cancer would be included as the bowel resection is the major procedure
- Bowel resection at the same time as emergency abdominal aortic aneurysm repair would not be included as the aneurysm repair is the major procedure

NELA Exclusion Criteria

Patients with the following characteristics will be excluded from NELA:

1. Patients under 18
2. Elective laparotomy / laparoscopy*

3. Diagnostic laparotomy/laparoscopy where no subsequent procedure is performed (NB, if no procedure is performed because of inoperable pathology, then include)
4. Appendicectomy +/- drainage of localised collection unless the procedure is incidental to a non-elective procedure on the GI tract
5. Cholecystectomy +/- drainage of localised collection unless the procedure is incidental to a non-elective procedure on the GI tract (All surgery involving the appendix or gallbladder, including any surgery relating to complications such as abscess or bile leak is excluded. The only exception to this is if carried out as an incidental procedure to a more major procedure. We acknowledge that there might be extreme cases of peritoneal contamination, but total exclusion avoids subjective judgement calls about severity of contamination.)
6. Non-elective hernia repair without bowel resection or division of adhesions
7. Minor abdominal wound dehiscence unless this causes bowel complications requiring resection
8. Non-elective formation of a colostomy or ileostomy as either a trephine or a laparoscopic procedure (NB: if a midline laparotomy is performed, with the primary procedure being formation of a stoma then this should be included)
9. Vascular surgery, including abdominal aortic aneurysm repair
10. Caesarean section or obstetric laparotomies
11. Gynaecological laparotomy (but see comment above about inclusion of gynae-oncology)
12. Ruptured ectopic pregnancy, or pelvic abscesses due to pelvic inflammatory disease
13. Laparotomy/laparoscopy for pathology caused by blunt or penetrating trauma
14. All surgery relating to organ transplantation (including returns to theatre for any reason following transplant surgery)
15. Surgery relating to sclerosing peritonitis
16. Surgery for removal of dialysis catheters
17. Laparotomy/laparoscopy for oesophageal pathology
18. Laparotomy/laparoscopy for pathology of the spleen, renal tract, kidneys, liver, gall bladder and biliary tree, pancreas or urinary tract
19. Returns to theatre for complications (eg bowel injury, haematoma, collection) following non-GI surgery are excluded i.e., returns to theatre following renal, urological, gynaecological, vascular, hepatic, pancreatic, splenic surgery are excluded. The specific exception to this list is that of complications requiring the assistance of a general surgeon after gynaecology-oncology surgery – these cases should now be INCLUDED, as per inclusion criteria above)

*Within CAMELOT, only procedures requiring a midline laparotomy (NOT laparoscopic only) will be included.

15.3 Appendix 3 – Definitions of postoperative morbidity

Postoperative complications are defined in accordance with StEP-COMPAC core outcome recommendations where possible (20). Additional investigations (e.g. microbiological tests, electrocardiographs, laboratory blood work) beyond those requested by the clinical team in the course of routine clinical care are not required. If an event meets one of the following definitions of a postoperative complication, the date of first onset will be recorded and its impact will be recorded in terms of:

1) Clavien-Dindo (CD) grading:

I. Any deviation from the normal postoperative course without the need for pharmacological, surgical, endoscopic or radiological intervention. Anti-emetics, anti-pyretics, diuretics, electrolytes or physiotherapy are not considered a deviation from the normal postoperative course.
II. Requires pharmacological treatment with drugs (including blood transfusion or total parenteral nutrition) other than those excluded from grade I.
III. Requires surgical, endoscopic or radiological intervention.
IV. Life-threatening complication (including CNS complication, but excluding transient ischaemic attack) requiring critical care admission
V. Death

2) Whether or not it meets the definition of a Serious Adverse Event (see: above). All complications of Clavien-Dindo grade IV or V automatically meet the definition of an SAE.

Patients are admitted to hospital prior to emergency laparotomy and may already have signs and symptoms of morbidity. Only complications with onset after the index laparotomy will be reported and analysed. The site principal investigator will confirm the presence and onset time of any complication. In cases where they are aware of study group allocation, this role should be delegated to another local investigator unaware of group allocation.

1. Postoperative complications to be analysed as secondary outcomes

Only complications with a severity of CDII or above will be analysed as secondary outcomes.

1.1 Postoperative Pulmonary Complications (PPC) (21)

PPC is a composite outcome defined as the occurrence of any of *atelectasis, pneumonia, Acute Respiratory Distress Syndrome* or *pulmonary aspiration* as defined below.

1.1.1 Atelectasis

Detected on computed tomography or chest radiograph

1.1.2 Pneumonia

Defined using US Centers for Disease Control criteria:

Two or more serial chest radiographs with at least **one** of the following **(one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease)**:

(i) New or progressive and persistent infiltrates,

(ii) consolidation,

(iii) cavitation;

AND at least **one** of the following:

(a) fever (>38°C) with no other recognised cause,

(b) leucopaenia (white cell count <4x10^9 litre^{-1}) or leucocytosis (white cell count >12x10^9 litre^{-1}),

(c) for adults >70 yr old, altered mental status with no other recognised cause;

AND at least **two** of the following:

(a) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements,

(b) new onset or worsening cough, or dyspnoea, or tachypnoea,

(c) rales or bronchial breath sounds,

(d) worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand).

1.1.3 Acute Respiratory Distress Syndrome (ARDS)

Berlin consensus definition:

Timing: within 1 week of a known clinical insult or new or worsening respiratory symptoms

AND chest imaging:

bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules

AND origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload (requires objective assessment, e.g. echocardiography, to exclude hydrostatic oedema),

AND oxygenation: mild PaO2:FiO2 between 26.7 and 40.0 kPa (200-300 mmHg) with PEEP or CPAP≥5cmH2O; moderate PaO2:FiO2 between 13.3 and 26.6 kPa (100-200 mmHg) with PEEP≥5cmH2O; severe PaO2:FiO2≤13.3 kPa (100 mm Hg) with PEEP≥5cmH2O.

1.1.4 Pulmonary aspiration

Defined by clear clinical history AND radiological evidence.

The following severity grading should be used for PPCs:

None (grade as CDI): planned use of supplemental oxygen or mechanical respiratory support as part of routine care, but not in response to a complication or deteriorating physiology. Therapies which are purely preventive or prophylactic for example high flow nasal oxygen or continuous positive airways pressure (CPAP) should be recorded as none.

Mild (grade as CDII): therapeutic supplemental oxygen <0.6 FiO_2

Moderate (grade as CDIII): therapeutic supplemental oxygen >0.6 FiO_2, requirement for high-flow nasal oxygen, or both

Severe (grade as CDIV): unplanned non-invasive mechanical ventilation, CPAP, or invasive mechanical ventilation requiring tracheal intubation

1.2 Respiratory failure (21)

This is a composite outcome of the occurrence of *either:*

1.2.1 ARDS

(see definition above),

OR

1.2.2 Mechanical ventilation

The need for need for tracheal re-intubation and mechanical ventilation after extubation, and within 30 days after surgery OR mechanical ventilation for more than 24 h after surgery.

1.3 Paralytic ileus (22)

Failure to tolerate solid food or defecate for three or more days after surgery.

1.4 Incisional surgical site infection (SSI) (23,24)

This should relate to the *midline laparotomy incision for the emergency laparotomy* and **not** any other wounds (e.g. incisions from an earlier elective procedure, secondary e.g. trochar wounds made during the same surgery as the midline laparotomy). Defined by the Centers for Disease Control as *either* of*:*

1.4.1 Superficial incisional SSI

Involves only skin and subcutaneous tissue of the incision AND the patient has at least **one** of the following:

a. purulent drainage from the superficial incision.

b. organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or nonculture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment.

c. superficial incision that is deliberately opened by a surgeon, treating doctor or designee* and culture or non-culture based testing of the superficial incision or subcutaneous tissue is not performed **AND** patient has at least one of the following signs or symptoms: localized pain or tenderness; localized swelling; erythema; or heat.

d. diagnosis of a superficial incisional SSI by a surgeon, treating doctor or designee*.

The following do **not** meet the definition of superficial incisional SSI:

- Diagnosis/treatment of cellulitis (redness/warmth/swelling), by itself, does not meet superficial incisional SSI criterion ‘d’.
- A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration).
- A localized stab wound or pin site infection; depending on the depth, these infections might be considered either a skin or soft tissue infection.

1.4.2 Deep incisional SSI

Involves deep soft tissues of the incision (for example, fascial and muscle layers) AND the patient has at least **one** of the following:

a. purulent drainage from the deep incision.

b. a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, treating doctor or designee* **AND** organism(s) identified from the deep soft tissues of the incision by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment *or microbiologic testing method is not performed.* (A microbiological test from the deep soft tissues of the incision that has a negative finding does not meet this criterion). **AND** patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness.

c. an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

* Designee may include nurse practitioner or physician’s assistant.

1.5 Rectus sheath catheter and local anaesthetic infusion-related complications

1.5.1 Rectus sheath catheter site bleeding or haematoma formation
Bleeding sufficient to require pharmacological (including blood/blood product) or surgical intervention should be recorded. Rectus sheath haematoma should be confirmed by imaging such as ultrasound or computed tomography.

1.5.2 Nerve damage
Temporary or permanent peripheral nerve injury affecting some or all terminal branches of the 9^{th}-11^{th} intercostal nerves. This may be characterised by ongoing sensory deficit in the relevant dermatomes after the expected regression of local anaesthetic effect. The diagnosis should be confirmed by a neurologist.

1.5.3 Local anaesthetic systemic toxicity
Clinical diagnosis based on suitable history and neurological (perioral tingling, tinnitus, slurred speech, tremor, confusion/agitation, convulsions, coma, respiratory depression) and/or cardiovascular symptoms (hypertension, tachycardia, hypotension, arrhythmias including sinus bradycardia, conduction blocks, ventricular tachy-arrhythmias, asystole).

1.5.4 Anaphylaxis to local anaesthetic
Severe, life-threatening, generalized or systemic hypersensitivity reaction, confirmed by immunological testing to have been caused by a local anaesthetic used for the intervention.

1.5.5 Rectus sheath catheter entrapment

Inability to easily remove catheter after use, typically due to entrapment by surgical suture material.

1.5.6 Skin reaction to rectus sheath catheter or adhesive dressing
Only skin reactions requiring pharmacological intervention should be recorded.

2. Other postoperative complications

2.1 Cardiovascular complications

2.1.1 Myocardial infarction (MI) (25,26)
Defined as either:
a) Acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of an increase or decrease in cardiac troponin (cTn) values with at least one value above the 99th percentile URL **AND** at least one of the following: (i) Symptoms of myocardial ischaemia (ii) New ischaemic ECG changes (iii) Development of pathological Q waves (iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology (v) Identification of a coronary thrombus by angiography or autopsy

OR:

b) Post-mortem demonstration of an acute atherothrombosis in the artery supplying the infarcted myocardium, regardless of cTn values

OR:

c) Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified.

2.1.2 Myocardial injury (25,26)
Detection of an elevated cTn value above the 99th percentile URL is defined as myocardial injury. The injury is considered acute if there is an increase or decrease in cTn values.

Note: it is not clinically possible to distinguish which increases of cTn levels are attributable to which mechanisms. A diagnosis of myocardial infarction requires an increase of cTn values and evidence of myocardial ischaemia that may be evident from the peri- and postoperative period (e.g. ST segment changes on telemetry/ ECG, repeated episodes of hypoxia, hypotension, tachycardia, or imaging evidence of myocardial injury). In the absence of evidence for acute myocardial ischaemia, the diagnosis is acute myocardial injury.

2.1.3 Non-fatal cardiac arrest (25)
Successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation

2.1.4 Pulmonary embolus (25)
Diagnosis of pulmonary embolism requires any **one** of the following:

(i) A high probability ventilation/ perfusion lung scan

(ii) An intraluminal filling defect of segmental or larger artery on a helical CT scan
(iii) An intraluminal filling defect on pulmonary angiography
(iv) A positive diagnostic test for deep venous thrombosis (e.g. positive compression ultrasound) and one of the following: (a) Non-diagnostic (i.e. low or intermediate probability) ventilation/perfusion lung scan (b) Non-diagnostic (i.e. subsegmental defects or technically inadequate study) helical CT scan

2.1.5 Deep vein thrombosis (25)
Diagnosis of deep venous thrombosis required any **one** of the following:
(i) A persistent intraluminal filling defect on contrast venography
(ii) Non-compressibility of one or more venous segments on B-mode compression ultrasonography
(iii) A clearly defined intraluminal filling defect on contrast enhanced CT

2.1.6 Atrial fibrillation (25)
New onset of irregularly irregular heart rate in the absence of P waves lasting at least 30 s or for the duration of the ECG recording (if <30 s)

2.1.7 Other cardiac arrhythmia (22)
ECG evidence of cardiac rhythm disturbance other than atrial fibrillation, and of new onset.

2.1.8 Cardiogenic pulmonary oedema (22)
Evidence of fluid accumulation in the alveoli due to poor cardiac function.

2.2 Renal complications

2.2.1 Acute kidney injury (AKI) (27,28)
AKI will be defined by the current KDIGO criteria, excluding the oliguric criteria. For the purposes of the CAMELOT trial, “baseline” SCr is the latest available SCr before the participant underwent surgery. AKI is defined as at least **one** of:

a) increase in serum creatinine (SCr) above baseline by ≥0.3 $mg.dl^{-1}$ (≥26.5 $\mu mol.L^{-1}$) within 48 hours,
OR
b) increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days,
OR
c) initiation of renal replacement therapy (RRT)

Initiation of RRT always indicates a CD grade IV or higher complication. Severity of AKI should also be classified according to KDIGO criteria, reflecting the highest SCr (or initiation of RRT) during the *entire AKI episode*:

Stage 1: SCr 1.5-1.9 times baseline **OR** an increase of ≥0.3 $mg.dl^{-1}$ (≥26.5 $\mu mol.L^{-1}$)
Stage 2: SCr 2.0-2.9 times baseline
Stage 3: SCr ≥3.0 times baseline **OR** increase in SCr to ≥4.0 $mg.dl^{-1}$ (≥353.6 $\mu mol.L^{-1}$) **OR** initiation of RRT.

2.3 Gastrointestinal complications

As with all adverse events, gastrointestinal complications should NOT include events that started before surgery e.g. bowel perforation or bleeding that were confirmed during the index laparotomy. Only record new events occurring in the postoperative phase.

2.3.1 Anastomotic breakdown (22)
Leak of luminal contents from a surgical connection between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicaemia, metabolic disturbance and/or multiple organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localised area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a subclinical leak.

2.3.2 Bowel infarction
Clinical diagnosis confirmed at subsequent laparotomy or presumed based on clinical suspicion supported by radiological imaging.

2.3.3 Perforated viscus
Clinical diagnosis demonstrated at subsequent laparotomy or confirmed by contrast enhanced radiograph or CT scan. For example, perforated bowel, gall bladder etc.

2.3.4 Gastrointestinal tract bleed
Gastrointestinal bleed is defined as unambiguous clinical or endoscopic evidence of blood in the gastrointestinal tract. Upper gastrointestinal bleeding (or haemorrhage) is that originating proximal to the ligament of Treitz, in practice from the oesophagus, stomach and duodenum. Lower gastrointestinal bleeding is that originating from the small bowel or colon.

2.4 Neurological complications

2.4.1 Stroke (22)
Embolic, thrombotic or haemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).

2.4.2 Transient ischaemic attack (29)
Transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

2.4.3 Postoperative delirium (30)
Postoperative delirium is defined as that which occurs in hospital up to one week post-procedure or until discharge (whichever occurs first) and meets **all** of the DSM-5 diagnostic criteria:

a. A disturbance in attention
b. The disturbance develops over a short period of time, represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day
c. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception)
d. The disturbances in a or c are not better explained by another pre-existing, established or evolving neurocognitive disorder and do not occur in severely reduced level of arousal such as coma

e. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct consequence of another medical condition, substance intoxication or withdrawal or exposure to a toxin or is due to multiple aetiologies *[for the purposes of the trial this criterion is fulfilled by the participant having undergone surgery and anaesthesia].*

2.5 Other infectious complications not defined previously

2.5.1 Organ/space surgical site infection (23)
Infection involves a part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure AND **one** of:

a. purulent drainage from drain in organ/space
b. organisms identified from aseptically-obtained fluid or tissue in the organ space by a culture or non-culture based testing method which is performed for the purposes of clinical diagnosis and treatment
c. an abscess or other evidence of infection involving the organ/space that is detected on gross histopathological exam
d. imaging test evidence suggestive of infection

2.5.2 Urinary tract infection (22)
A positive urine culture of ≥10^5 colony forming units/mL with no more than two species of micro-organisms with at least **one** of the following symptoms or signs: fever (>38 °C), urgency, frequency, dysuria, supra-pubic tenderness, costo-vertebral angle pain or tenderness with no other recognised cause, identified within a 24-hour period.

Alternatively, the patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation, or during a histopathologic examination with **one** of the following:

a) purulent drainage from affected site;
b) radiographic evidence of infection;
c) physician diagnosis of infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space;
d) physician institutes antibiotic therapy for an infection of the kidney, ureter, bladder, urethra, or surrounding tissues.

2.5.3 Laboratory confirmed blood stream infection (22)
An infection which meets at least **one** of the following criteria but is not related to infection at another site:

Patient has a recognised pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site

OR
Patient has at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least **one** of the following:

a) common skin contaminant cultured from two or more blood cultures drawn on
b) separate occasions
c) common skin contaminant cultured from at least one blood culture from a
d) patient with an intravascular line, and the physician institutes antimicrobial
e) therapy

f) positive blood antigen test

2.5.4 Infection, source uncertain
An infection which is considered likely to be one of the following but cannot be differentiated because clinical information suggests more than one possible site: superficial surgical site infection, or deep surgical site infection, or organ/space surgical site infection, or pneumonia, or urinary tract infection, or laboratory confirmed blood stream infection.

There must be a strong clinical suspicion of infection meeting **two or more** of the following criteria:
1. Core temperature <36°C or >38°C
2. White cell count >12 x $10^9.L^{-1}$ or <4 x $10^9.L^{-1}$
3. Respiratory rate >20 breaths per minute or PaCO2 <35 mmHg
4. Pulse rate >90 beats per minute

2.5.5. SARS-CoV-2/COVID-19 infection
Confirmed by lateral flow test or PCR. Date of onset should be recorded as the date of the confirmatory positive test. The absence or presence of symptoms should be recorded.

2.6 Other respiratory complications not defined previously

2.6.2 Pleural effusion
Confirmed by computed tomography, chest X-ray or ultrasound.
2.6.3 Pneumothorax
Confirmed by computed tomography, chest X-ray or ultrasound.
2.6.4 Bronchospasm
Diagnosed clinically.

2.7 Other complications

2.7.1 Multi-organ dysfunction syndrome (MODS), cause uncertain
A life threatening but potentially reversible physiologic derangement involving failure of two or more organ systems not involved in the primary underlying disease process. This classification should only be used following adjudication of the local Principal Investigator that despite all available clinical and diagnostic information there is no clear unifying cause for the MODS. In all other cases the event should be classified by the causative process and its severity rated as CD IV or higher.

2.7.2 Electrolyte disturbance
Abnormal levels of plasma electrolytes considered to be clinically significant and requiring treatment.

2.7.3 Other (non-gastrointestinal tract) postoperative haemorrhage
Blood loss within 72 hours after the start of surgery which would normally result in transfusion of blood.

2.7.4 Anaphylaxis (not related to local anaesthetic)
Severe, life-threatening, generalized or systemic hypersensitivity reaction.

3. Postoperative interventions required within the index postoperative hospital admission

Red blood cell transfusion Y/N
Parenteral (intra-venous) nutrition Y/N
Endoscopic or radiological intervention Y/N
Repeat surgery after the index laparotomy Y/N

- If YES please indicate whether this was:
  - Planned
  - Unplanned (with primary indication)

Unplanned critical care admission from a ward (level 1 care) to treat a complication Y/N
Planned critical care admission prolonged to treat a complication Y/N
Total duration of postoperative invasive mechanical ventilation
Total duration of postoperative non-invasive ventilation (CPAP, BiPAP)